



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.

Apigenin

Evidence Summary

Preclinical evidence suggests strong antioxidant, anti-inflammatory, and anti-neoplastic effects, but no clinical trials have directly tested apigenin; it is generally safe, but may interfere with drug metabolism.

Neuroprotective Benefit: No clear evidence in humans yet, but preclinical studies suggest apigenin has pro-cognitive, neuroprotective, neurogenic, antioxidant, and anti-inflammatory effects.

Aging and related health concerns: Many preclinical studies have shown potential for protection against cancer, cardiovascular disease, and diabetes, but observational studies in humans are mixed, and no clinical trials have specifically tested apigenin.

Safety: Apigenin is abundant in some vegetables and herbs and is considered safe, but excessive amounts may cause drug interactions due to inhibition of CYP2C9, an enzyme responsible for metabolism of many drugs.

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|---|--|--|
| Availability: OTC and in diet | Dose: Diet rich in fruits/vegetables are sufficient for general health. Supplementation of 3-10 mg/kg, p.o. may have calming effects. | Chemical formula: C ₁₅ H ₁₀ O ₅ MW: 270.24 |
| Half life: 91.8 hrs | BBB: penetrant | |
| Clinical trials: 3 that included apigenin (not apigenin alone); total of 161 people. | Observational studies: 3 that included a total of 105,435 people examining dietary apigenin intake. | |

What is it? Apigenin is a flavone found in many plants and fruits and is rich in celery, yarrow, tarragon, cilantro, basil, and oregano. It is also abundant in chamomile tea, red wine, and beer. Apigenin exerts anxiolytic effects at high doses by inhibiting NMDA receptors [1]; it also has affinity to GABA-A receptors [2]. Apigenin also exerts potent antioxidant activities by scavenging free radicals and upregulating glutathione levels; it also exerts anti-inflammatory effects [3; 4; 5]. Apigenin is most studied for its potential anti-cancer properties [5].

Neuroprotective Benefit: No clear evidence in humans yet, but preclinical studies suggest apigenin has pro-cognitive, neuroprotective, neurogenic, antioxidant, and anti-inflammatory effects.

Types of evidence:

- 1 open-label clinical study testing a combination therapy
- 1 randomized controlled trial testing parsley supplementation on oxidative stress markers
- Numerous reviews
- Numerous laboratory studies

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

None available.



Human research to suggest benefits to patients with dementia:

No studies have tested apigenin alone in patients with dementia. One open-label clinical study (article in Spanish) tested a combination therapy including apigenin (100 mg), ferulic acid (50 mg), gamma oryzanol (50 mg), and silymarin (150 mg) in patients with Alzheimer's, Parkinson's, and multiple sclerosis [6]. The combination was aimed to control apoptosis (ferulic acid; gamma oryzanol), oxidative stress (silymarin), abnormal deposits of metals and proteins, and pathophysiological enzymatic pathways (caspases and MAPK systems; apigenin). The capsule was taken orally twice daily in 12 Alzheimer's patients, 17 Parkinson's patients, and 13 multiple sclerosis patients. In Alzheimer's disease patients, clinical stabilization was achieved in all 12 patients and 9 patients showed an improvement on the mini-mental test score. In multiple sclerosis patients, clinical stabilization was achieved in all 13 patients with improvement on the Expanded Disability Status Scale in 4 patients (40%). In Parkinson's disease patients, clinical stabilization was shown in all 17 patients with improvements on the Unified Parkinson's Disease Rating Scale in 15 out of 17 (88.2%). Because there was no placebo control, the results may be biased. Also, assuming the treatment was effective, it is unknown which compounds are responsible for the positive effects. This study was published in 2010, but there have not been any follow-ups on the potential of this combination therapy, or the mechanisms behind potential synergistic effects.

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

Numerous preclinical studies have suggested multiple potential mechanisms of action for apigenin's neuroprotective properties. Apigenin does cross the blood-brain-barrier [7]. A randomized controlled trial of 14 healthy volunteers showed that parsley supplementation for 2 weeks resulted in increased antioxidant capacity in the plasma (by increasing activities of erythrocyte glutathione reductase and superoxide dismutase) [8].

Apigenin treatment has shown pro-cognitive effects in rodent models of Alzheimer's disease [9; 10], diabetes [11], stroke [12], and isoflurane-induced cognitive dysfunction [13].

In rodent models of Alzheimer's disease, apigenin treatment (20-40 mg/kg) resulted in improved learning and memory, improved antioxidative activity, downregulation of BACE1 enzyme (involved in the process of beta-amyloid generation), reduced fibrillary amyloid deposits, maintenance of the neurovascular unit integrity, modulation of microvascular function, increased regional cerebral blood flow, increased acetylcholine levels, inhibition of AChE (which breaks down acetylcholine), and restoration of the ERK/CREB/BDNF pathway involved in neuroprotection and neurogenesis [9; 10]. In a study using iPSC-derived neurons from Alzheimer's patients, apigenin had potent anti-inflammatory properties with the ability to protect neurites and cell viability by downregulating cytokine and nitrous



oxide release in inflammatory cells and reducing caspase-3/7-mediated apoptosis [14]. A cell culture study also showed that apigenin protected neurons against A β -mediated toxicity by preserving mitochondrial function (by relieving mitochondrial membrane dissipation), regulating redox imbalance (by increasing glutathione levels and endogenous antioxidant enzyme activities), and inhibiting apoptosis [15].

In an *in-vitro* and *in-silico* screening study of natural flavonoids, apigenin, myricetin, quercetin, kaempherol, and morin directly inhibited BACE1 enzyme [16]. However, apigenin did not affect neuronal BACE1 activity and did not reduce neuronal A β species production.

In normal 7-week old mice, administration of apigenin (25 mg/kg) for 10 days resulted in improved memory and increased neurogenesis in the hippocampus [17].

In Parkinson's disease models, apigenin treatment exerted potent antioxidant activity (increased endogenous antioxidant activities like glutathione and SOD) and promoted expression of the neurotrophic factor BDNF while decreasing apoptosis (caspase-3 and 9) and inflammatory markers (GFAP, TNF- α , IL-6)[18; 19; 20].

In a model of spinal cord injury, apigenin pretreatment (10-20 mg/kg) showed neuroprotective effects by reducing markers of inflammation and apoptosis (IL-1 β , TFN- α , ICAM-1 and caspase-3), with higher ratio of anti-apoptosis: pro-apoptosis markers (Bcl-2:Bax) [21].

In a rat model of post-stroke cognitive deficits, apigenin treatment (40 mg/kg) improved cognitive functions while decreasing histone deacetylase (HDAC) content and increasing BDNF [12]. A study in a rat model of isoflurane-induced cognitive dysfunction also reported that apigenin restored cognitive function by restoring histone acetylation and suppressing neuroinflammation (NF κ B signaling) [13].

Apigenin inhibits glutamate NMDA receptors and confers neuroprotection against glutamate-induced neurotoxicity [1]. In hippocampal cultures, apigenin inhibits glutamate release from nerve terminals [22]. Inhibition of NMDA receptors is the mechanism of action for the Alzheimer's drug memantine (NMDA receptor antagonist).

In a high throughput screening system for anti-inflammatory and neuroprotective compounds, apigenin was one of the most potent polyphenolic compounds to protect neurons against microglial insult [23]. An *in vitro* study of plant-derived polyphenols also reported that apigenin and diosmetin were the



strongest inhibitors of nitric oxide production induced by advanced glycation endproducts (AGE); apigenin, diosmetin, and silymarin also reduced TNF- α expression [24]. Cell culture studies have also reported that apigenin exerts anti-inflammatory effects by suppressing IFN γ -induced CD40 expression in microglia while also decreasing TNF α and IL6 production [25].

APOE4 interactions: Unknown.

Aging and related health concerns: Many preclinical studies have shown potential for protection against cancer, cardiovascular disease, and diabetes, but observational studies in humans are mixed, and no clinical trials have specifically tested apigenin.

Types of evidence:

- 3 clinical trials testing dietary interventions that included apigenin
- 3 observational studies examining dietary intake of flavonols and flavones
- Numerous laboratory studies

Cancer: MIXED. In a prospective cohort study of 38,408 women from the Women's Health Study, who were followed for 11.5 years, no significant associations were found between intake of flavonol/flavone-rich foods and incidence of total or specific cancers [26]. Relative risks (RRs) in the highest quintile compared to lowest quintile were 1.03 for breast cancer, 1.01 for colorectal cancer, 1.03 for lung cancer, 1.15 for endometrial cancer, and 1.09 for ovarian cancer.

However, a larger prospective cohort study of 66,940 women from the Nurses' Health Study reported that there is a trend for *increased* incidence of ovarian cancer with increased apigenin intake ($p=0.03$), though quintile-specific RRs were not statistically significant [27]. The result may be due to chance based on the absence of a trend across quintiles of intake. Additional prospective studies are needed.

In contrast to the two studies above, a smaller study suggested potential protection. In a prospective cohort study of patients with resected colon cancer, those treated with flavonoid mixture (20 mg apigenin and 20 mg EGCG/day) had no recurrence (0/14) and one adenoma development, while the cancer recurrence rate of the 15 matched untreated controls was 3/15 (20%) and adenomas evolved in 4 of those patients [28]. Long-term treatment with a flavonoid mixture may reduce recurrence rate of colon neoplasia, though larger studies that are randomized and placebo-controlled will need to be carried out to confirm these preliminary findings.



In a network pharmacology-based virtual screening of a library of natural compounds, apigenin 7-glucoside (sugar-bound form of apigenin found in plants) had strong binding interactions with 17 cancer drug targets, suggesting that apigenin derivatives have cancer drug-like activities [29].

In a cell culture and mouse study of colon cancer, apigenin administration sensitized colon cancer cells to antitumor activity of ABT-263 (Navitoclax) by inhibiting expression of a protein involved in drug-resistance (Mcl-1) and suppressing prosurvival regulators (AKT and ERK) [30]. Apigenin dramatically enhanced ABT-263-induced cancer cell death.

Several preclinical studies have reported that apigenin inhibits cancer cell proliferation and tumor angiogenesis by inhibiting the transcription factor hypoxia-inducible factor (HIF-1 α) and a growth factor (VEGF) involved in blood vessel formation [31; 32].

Diabetes: NO BENEFIT/MIXED. A prospective study of 38,018 women followed for an average of 8.8 years reported that dietary intake of total flavonols and flavones, or individual ones (quercetin, kaempferol, myricetin, apigenin, and luteolin) was not significantly associated with risk of type 2 diabetes [33]. In a subcohort of 344 nondiabetic women, the total intake of flavonols and flavones was not significantly related to plasma concentrations of fasting insulin, HbA(1C), or inflammatory markers (CRP and IL-6).

However, in a rat model of diabetes, apigenin reduced blood glucose levels, improved cognitive function, decreased oxidative stress indicators (MDA), and increased antioxidant capacity (increased glutathione and SOD activity) in the cerebral cortex and hippocampus [11].

Cardiovascular: MIXED. In a randomized controlled trial of 18 healthy volunteers, 5 g of dried parsley/day providing 84 mg of apigenin/day did not have significant effects on platelet aggregation, thromboxane B2 production, factor VII, or other hemostatic variables [34]. The anti-aggregatory effects of flavonoids seen *in vitro* may be due to concentrations that cannot be attained *in vivo*. It is also possible that dietary flavonols and flavones modulate cardiovascular risk, but potential benefits do not appear to be mediated by hemostatic variables.

In a mouse model of hyperlipidemia, apigenin and simvastatin treatment for 28 days significantly reduced total cholesterol, LDL cholesterol, and triglyceride levels [35]. Apigenin appears to regulate cholesterol metabolism by promoting cholesterol absorption and conversion, and accelerating reverse



cholesterol transport. An *in vitro* experiment showed that apigenin plays a role in resisting oxidation and protecting blood vessels by increasing antioxidant (SOD) activity and nitric oxide secretion.

Obesity: POTENTIAL BENEFIT. In a mouse model of high fat diet-induced obesity, apigenin (0.005% w/w) supplementation lowered plasma levels of free fatty acid, total cholesterol, and hepatic dysfunction markers, and ameliorated fatty liver disease and liver enlargement (hepatomegaly) [36]. These effects were partly attributed to increased expression of genes regulating fatty acid oxidation, tricarboxylic acid cycle, oxidative phosphorylation, electron transport chain, and cholesterol homeostasis, and decreased activities of enzymes responsible for triglyceride and cholesterol synthesis in the liver. Apigenin also lowered plasma levels of pro-inflammatory mediators and fasting blood glucose. In a different study of mice receiving a high-fat diet, apigenin and simvastatin treatment for 28 days reduced body weight [35].

Stress: POTENTIAL BENEFIT. In a rat model of chronic unpredictable mild stress, apigenin treatment for 3 weeks (20 mg/kg) ameliorated behavioral abnormalities [37]. Apigenin treatment resulted in antidepressant-like effects in these rats by inhibiting inflammation (e.g., IL-1 β production and NLRP3 inflammasome expression) via the up-regulation of PPAR γ expression. In mice receiving chronic corticosterone administration, apigenin treatment (20 and 40 mg/kg) reversed the behavioral changes while increasing levels of the neurotrophic factor BDNF in the hippocampus [38]. No studies in humans have corroborated these findings.

Safety: Apigenin is abundant in some vegetables and herbs and is considered safe, but excessive amounts may cause drug interactions due to inhibition of CYP2C9, an enzyme responsible for metabolism of many drugs.

Types of evidence:

- 1 randomized controlled trial of parsley supplementation
- Multiple reviews
- Several laboratory studies

Apigenin is considered very safe and no toxicity has been observed even at high doses in rodent studies [5]. In a study in mice, there was a 26% to 48% reduction in locomotor activity at 30 and 100 mg/kg, suggesting mild sedation [39]. While apigenin had some anxiolytic and sedative effects, it did not act as an anticonvulsant or myorelaxant even at high doses (up to 80 mg/kg).

Drug interactions: There is no entry for apigenin on Drugs.com or WebMD.com. However, apigenin is a potent inhibitor of CYP2C9 [40], an enzyme responsible for metabolism of many drugs, and therefore excessive apigenin intake may significantly increase the effects/toxicities of such drugs (e.g., NSAIDs, fluvastatin, sulfonyleureas, irbesartan, losartan, warfarin, sildenafil, amitriptyline, fluoxetine, rosiglitazone, tamoxifen, montelukast, polyunsaturated fatty acids, etc.).

Sources and dosing: Apigenin is a flavone found in many plants and fruits. It is particularly rich in celery, yarrow, tarragon, cilantro, coneflower, licorice, flax, spearmint, basil, and oregano. It is also abundant in chamomile tea, red wine, and beer. Apigenin is one of the active ingredients in *Bacopa monnieri*. Apigenin is also available as a supplement in capsule form, often containing 50 mg per capsule. Chamomile supplements in capsule form typically contain small amounts (1-2%) of apigenin. According to Examine.com, doses found in a diet rich in fruits and vegetables are adequate for general well-being. Supplementation in the range of 3-10 mg/kg may have anxiolytic effects.

Research underway: No clinical trials are currently testing apigenin for cognitive aging or dementia. One clinical trial to test a flavonoid supplement (20 mg apigenin and 20 mg EGCG/day) in prevention of colonic neoplasia was started in 2008 but suspended in 2012 ([NCT00609310](https://clinicaltrials.gov/ct2/show/study/NCT00609310)). An ongoing clinical trial is testing an apigenin-rich celery-banana bread in high risk breast clinic patients ([NCT03139227](https://clinicaltrials.gov/ct2/show/study/NCT03139227)). The outcome measures are apigenin levels in blood and urine. This trial is currently recruiting patients.

Search terms:

Pubmed, Google: apigenin

- + Alzheimer's, + dementia, + cognitive, + neurogenesis, + ApoE, + clinical trial, + meta-analysis, + sleep, + cholesterol, + angiogenesis, + lifespan, + safety, + adverse effects

Websites visited for apigenin:

- Clinicaltrials.gov
- Examine.com
- Treato.com (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com
- DrugBank.ca
- Labdoor.com (0)

- ConsumerLab.com (0)

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