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## Genistein

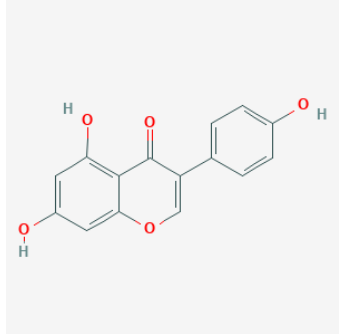
### Evidence Summary

Genistein intake via diet or supplementation may protect against some cancers, diabetes, and cognitive decline, though more studies are needed that test genistein specifically.

**Neuroprotective Benefit:** No studies have tested genistein specifically, but soy isoflavone interventions that include genistein have improved a few cognitive functions. Benefits may depend on sex and age.

**Aging and related health concerns:** Higher genistein intake may be protective against some cancers and diabetes.

**Safety:** Genistein intake via diet or supplementation is generally regarded as safe.

<b>Availability:</b> OTC and in diet (soy).	<b>Dose:</b> 50-54 mg/day of genistein to prevent diabetes	<b>Chemical formula:</b> C <sub>15</sub> H <sub>10</sub> O <sub>5</sub> <b>MW:</b> 270.24  Source: <a href="#">Pubchem</a>
<b>Half life:</b> 9 hours	<b>BBB:</b> permeable	
<b>Clinical trials:</b> a meta-analysis of 7 RCTs including a total of 670 subjects	<b>Observational studies:</b> multiple meta-analyses based on dietary intake or biomarker studies, with hundreds of thousands of people	

**What is it?** Genistein is an isoflavonoid derived from soy products. The whole soybean contains approximately equal amounts of genistein and daidzein, with smaller amounts of glycitein. Genistein has drawn attention for its action on the estrogen receptor (ER)  $\beta$ , which has been a promising therapeutic target for cognitive impairment, menopausal symptoms, and premenstrual syndrome (PMS) [1] ([WebMD.com](#)). It is selective for ER $\beta$  [1], and not ER $\alpha$ , which is associated with the classical effects of estrogen, including promoting breast and reproductive organ cancers. Genistein and other soy isoflavones have also been studied for preventing high cholesterol and high blood pressure.

**Neuroprotective Benefit:** No studies have tested genistein specifically, but soy isoflavone interventions that include genistein have improved a few cognitive functions. Benefits may depend on sex and age.

Types of evidence:

- 1 randomized controlled trial of soy isoflavone treatment in Alzheimer's patients
- 1 observational study
- Numerous laboratory studies

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

No clinical trial has tested genistein specifically. Many have examined the effects of isoflavone treatments in menopausal women (see Soy Isoflavone report for details).



A longitudinal study (Study of Women's Health Across the Nation; SWAN) compared 195 Japanese and 185 Chinese women to examine whether dietary isoflavone intake was associated with measures of cognitive performance [2]. The study concluded that genistein intake was not significantly associated with measures of cognitive performance in either ethnic group. Median intakes of genistein (ug/day) were 6,788 for Japanese, 3,534 for Chinese, 3.6 for Caucasian, 1.7 for African American, and 0 for Hispanic women.

Human research to suggest benefits to patients with dementia:

No studies have tested genistein specifically. A randomized controlled trial of 59 Alzheimer's disease patients reported that soy isoflavone treatment (Novasoy brand; 100 mg/day, of which approximately 85% was daidzin and genistin as glycosides) for 6 months did not significantly improve cognitive function over placebo, despite increased plasma levels of isoflavones [3].

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

There are numerous potential mechanisms of action for neuroprotection. The primary mechanism of action of genistein is on ER $\beta$ , where it acts as an agonist with 30-fold greater affinity compared to ER $\alpha$  [1]. ER $\beta$  is expressed in brain regions important for executive function and memory, and its stimulation can lead to improved cognitive functions in preclinical studies [4]. Genistein exhibits antioxidant properties by increasing antioxidant enzymes and glutathione, reducing free radicals, and inhibiting mitochondrial dysfunction [5]. In a review of phytochemicals, genistein (along with others such as curcumin, resveratrol, pterostilbene, etc.) was reported as a potent NF-kB inhibitor that may be relevant for Alzheimer's treatment [6].

Many preclinical studies have evaluated the effects of genistein. Cognitive benefits of genistein have been observed in a rat model of isoflurane-induced neurotoxicity [7], rat and mouse models of LPS-induced cognitive impairment [8; 9], diabetes-induced cognitive decline [10], a mouse model of Parkinson's [11], and Alzheimer's models [12; 13]. In these studies, genistein inhibited apoptosis (reduced Bad, Bax, caspase-3) [7; 13], increased anti-apoptotic factors (Bcl-2, Bcl-xL) [7], upregulated neurotrophic/BDNF signaling (CREB/TrkB/BDNF) [7; 8], decreased acetylcholine esterase (enzyme that breaks down acetylcholine) activity [9], lowered inflammatory markers (IL6, NF-kB, TNF $\alpha$ , COX2, iNOS, GFAP) [9; 10], and increased an antioxidant factor (Nrf2) [9].



In contrast to studies showing cognitive benefits with genistein, one study of rats that had undergone ovariectomy (removal of ovaries) reported that genistein treatment (162-323 µg/kg/day in pellet form) impaired performance on a working memory task, especially in aged rats [14]. Another study of ovariectomized rats showed that genistein treatment (40 mg/kg) resulted in improvement in spatial memory in young but not aged rats [15].

In preclinical Alzheimer's models including cell cultures, genistein decreases Aβ levels [12] and inhibits neuronal apoptosis induced by Aβ [16].

*APOE4 interactions:* No interactions between genistein and APOE4 have been found so far.

**Aging and related health concerns:** Higher genistein intake may be protective against some cancers and diabetes.

*Types of evidence:*

- 3 meta-analyses or systematic reviews of randomized controlled trials
- 5 meta-analyses or systematic reviews of observational studies (on diet, blood levels, or urinary levels of genistein)
- 1 double-blind randomized controlled trial
- 2 observational studies
- Numerous laboratory studies

**Lifespan:** NULL/MIXED. In a case-control study of Japanese people aged 70 and older, serum levels of genistein (or daidzen) were not associated with disability or death [17]. In a study based in the US, no associations with mortality were found for urinary genistein levels [18].

A study in *C. elegans* reported that genistein increased lifespan by 28% under normal conditions and up to 68.4% in a stressful environment (thermotolerance test at 36°C) [19]. The genistein-mediated increase in stress tolerance was partly attributed to increased expressions of stress resistance proteins (SOD-3 and HSP-16.2). Genistein did not induce significant changes in food intake, reproduction, or growth, but did lead to an up-regulation of locomotor ability, suggesting enhanced healthspan in this species.

In contrast, a study in *Drosophila* flies showed that genistein dose-dependently reduced mean and maximum life span of both male and female flies compared to controls [20]. The highest dose (10



uM/100 mL medium) resulted in a mean lifespan reduction of 42.5% and 43.6% in males and females, respectively.

**Prostate cancer:** POTENTIAL BENEFIT. A new 2018 meta-analysis of 30 observational studies in men reported that the pooled RR of prostate cancer for high vs low genistein intake was 0.84 (95% CI, 0.73-0.97) [21]. Other large meta-analyses of numerous observational studies also showed protective benefit of genistein with OR ranging between 0.81-0.87 [22; 23] while one study found no associations [24]. In a subgroup analysis stratified by population, genistein showed preventive benefits on prostate cancer risk in Asian populations but not in Western populations [22]. Potential mechanisms of protective action include agonist activity of estrogen receptors, antioxidant activity, cell cycle inhibition, anti-angiogenesis, inhibition of TNF $\alpha$ , and induction of apoptosis in prostate cancer cells [25].

**Breast cancer:** POTENTIAL BENEFIT. A 2017 meta-analysis of 40 observational studies examining isoflavone biomarkers (in plasma, serum, or urine) reported that higher genistein concentrations were associated with a 28% lower risk of breast cancer (OR=0.72; 95% CI, 0.54-0.96) [24].

**Colorectal cancer:** POTENTIAL BENEFIT. A 2017 meta-analysis of 2 case-control studies reported that high plasma levels of genistein was associated with decreased colorectal cancer risk in both Korean and Vietnamese population [26]. The Korean population had an OR of 0.50 (95% CI, 0.25-0.98) while the Vietnamese population had an OR of 0.43 (95% CI, 0.25-0.73). It is unclear whether these preventive benefits also occur in Western populations.

**Cardiovascular:** POTENTIAL BENEFIT. A meta-analysis of 8 randomized controlled trials in postmenopausal women testing the effects of genistein (40-54 mg/day) for 6-36 months reported that genistein significantly increased HDL cholesterol levels (+4.9 mg/dl) [27]. A subgroup analysis revealed that in postmenopausal women with metabolic syndrome, genistein also decreased LDL cholesterol (-16.90 mg/dl), total cholesterol (-15.83 mg/dl), and triglycerides (-46.58 mg/dl). These effects were not seen in women who did not have metabolic syndrome. Independent of the effect of genistein, replacing some animal proteins with soy protein (e.g., tofu, edamame, etc.) should improve cardiovascular health [28].

**Type 2 diabetes:** BENEFIT. A 2017 meta-analysis of 7 randomized controlled trials (670 subjects total) reported that genistein treatment (54 mg/day for most, one study at 50 mg/day) for 6-36 months had a significant effect in lowering fasting glucose levels [29]. The average difference in fasting glucose levels between the genistein and placebo groups was -6.35 mg/dL (95% CI, -10.78 to -1.93 mg/dL). Genistein



was more effective than placebo in reducing fasting insulin and improving insulin resistance (HOMA-IR difference, -0.74, 95% CI, -1.21 to -0.28).

A 2017 meta-analysis of 40 observational studies examining isoflavone biomarkers (in plasma, serum, or urine) reported that higher genistein concentrations were associated with a 21% decreased risk for diabetes (OR=0.79, 95% CI, 0.62-0.99) [24]. Other meta-analyses have shown more modest effects, with one from 2016 that included 163,457 people showing a 9% reduction in diabetes risk (HR=0.91, 95% CI, 0.85-0.98) when comparing the highest quintile of genistein with the lowest [30].

In preclinical studies, genistein increased  $\beta$ -cell mass and proliferation, increased insulin secretion and glucose tolerance, and decreased hyperglycemia by activation of several pathways (cAMP-PKA-dependent ERK1/2 signaling pathway, CAMKII and calcium signaling, decreased NF- $\kappa$ B pathway) [31].

**Homocysteine:** DECREASED. Higher homocysteine levels are associated with a higher risk of developing a variety of age-related diseases, while supplementing with vitamins B6, B9 (folate), and B12 can reduce homocysteine levels [32]. A meta-analysis of 8 randomized controlled trials testing the effects of genistein (40-54 mg/day) for 6-36 months reported that genistein was effective in reducing plasma levels of homocysteine by 0.58  $\mu$ M/L [27].

**Osteoporosis:** MIXED/POTENTIAL BENEFIT. In a systematic review of 23 double-blind randomized controlled trials of soy isoflavone interventions, there were 5 trials that evaluated the effects of genistein specifically and found that 3 of them showed no benefit while 2 studies showed protective benefit in bone density markers [33]. A randomized controlled trial of 121 postmenopausal women (not included in the above systematic review) reported that genistein aglycone tablets (54 mg/day) co-prescribed with calcium and vitamin D3 supplements showed increased mean bone mineral density, and a lower percentage of women (12%) had osteoporosis after 2 years compared to those receiving placebo (31%).

Preclinical studies suggest that genistein may activate ER $\beta$  in osteoblasts [28]. Because it inhibits a tyrosine kinase, it can inhibit cell growth and osteoclast activity. Together, genistein may suppress bone resorption and minimize bone loss.



**Safety:** Genistein intake via diet or supplementation is generally regarded as safe.

*Types of evidence:*

- 1 meta-analysis based on 7 randomized controlled trials
- 4 clinical trials that tested soy isoflavone interventions that included genistein
- 1 extensive toxicity and carcinogenesis study in rats (242 pages)

Most safety evidence for genistein comes from large studies with soy isoflavones or dietary consumption of soy products. The largest study that examined the effects of genistein specifically was a meta-analysis of 7 randomized controlled trials including a total of 670 subjects [29]. This study reported that genistein at a dose of 54 mg/day was not associated with any significant adverse effect on the uterus, endometrial thickness, or breast density. One long-term study of 3 years reported that there were no significant differences between genistein and placebo groups on breast density after 2 or 3 years of treatment. In long-term trials, about 19% of subjects reported gastrointestinal symptoms.

Other individual randomized controlled trials, including one in Alzheimer's patients, reported good safety profiles with soy isoflavone interventions [3; 34; 35; 36]. Adverse events were generally mild [35] and no abnormal lab values were observed [3].

In an extensive toxicity and carcinogenesis study by the National Toxicology Program (242 pages long), no evidence of carcinogenicity was found after 2 years of genistein treatment in male rats, even at the highest dose (500 ppm in feed, equivalent to 44 mg/kg/day) [37]. In female rats, continuous ingestion of genistein for 2 years did not alter tumor rates except at the highest dose (500 ppm in feed, equivalent to 37 mg/kg/day) at which there was increased pituitary adenoma/adenocarcinoma (32.7% compared to 16.7% in controls) and decreased benign mammary fibroadenoma (24.5% compared to 59.3% in controls). Because 500 ppm (37 mg/kg/day) is equivalent to a human daily dose of 325 mg/day for someone weighing 120 lbs, these findings are not too concerning unless you ingest doses that are 6-7 times what is typically recommended for menopausal women.

[Treato.com](https://www.treato.com) rates genistein a 4.4 out of 5 stars. As of January 5, 2018, there have been 281 concerns from 3,655 posts, 181 of which were for tumors, 104 on weakness, 59 on hair loss, 49 on osteoporosis, and 46 on acne. Most users were using genistein supplements for menopausal symptoms (hot flashes and night sweats).



*Drug interactions:* Drug interactions with genistein are not well-documented ([Drugs.com](#)). Because genistein binds to estrogen receptors, it will likely interact with drugs that target the estrogen system.

**Sources and dosing:** Genistein can be found in food sources such as soybeans, tofu, fava beans, kudzu, and lupin ([DrugBank](#)). It is also available as supplements in tablet and capsule forms. Doses that showed improvement in some cognitive domains in clinical studies ranged from 60-100 mg of soy isoflavones/day (genistein doses of ~52 mg/day) [[36](#); [38](#); [39](#)]. However, soy isoflavone doses of 100 mg/day for 6 months did not improve cognitive function in Alzheimer's patients [[3](#)].

Genistein is typically found as genistin, a sugar-bound form that is biologically inactive. During high-temperature heating (a common process in Eastern Asia), genistin is reduced to a smaller, simple glycoside that can be broken down in the small intestine to genistein aglycone, which is bioavailable [[40](#)].

**Research underway:** Several clinical trials are ongoing. One double-blind randomized controlled trial is testing the effects of genistein treatment on amyloid beta levels in the cerebral spinal fluid of Alzheimer's disease patients ([NCT01982578](#)). The intervention is 60 mg of genistein twice daily for 180 days. The study is scheduled to be completed in 2018. There are other clinical trials that are testing the effects of genistein on prostate cancer ([NCT02766478](#); [NCT01126879](#)), bladder cancer ([NCT01489813](#)), and head and neck cancer ([NCT02075112](#)). There is also a phase 2 study that is ongoing testing the effects of genistein in pediatric oncology patients ([NCT02624388](#)).

#### Search terms:

Pubmed, Google: Genistein

- + cognitive, + Alzheimer's, + ApoE, + clinical trial, + randomized trial, + meta-analysis, + Cochrane, + lifespan, + longevity, + mortality, + breast cancer, + safety, + adverse effects

Websites visited for genistein:

- [Clinicaltrials.gov](#)
- [Treato.com](#)
- [DrugAge](#) (1)
- [Geroprotectors](#) (1)
- [Drugs.com](#)
- [WebMD.com](#)
- [PubChem](#)

- [DrugBank.ca](#)
- Labdoor.com (0)
- [ConsumerLab.com](#)
- [Patientslikeme](#)
- Cafepharma (3)

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