



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.

Genistein

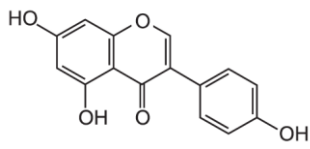
Evidence Summary

Clinical trials have shown that genistein treatment improves cholesterol, insulin/glucose, HOMA-IR, and homocysteine levels. But in the US, higher urinary genistein levels are associated with higher mortality.

Neuroprotective Benefit: Soy isoflavone interventions that include genistein have improved a few cognitive functions, but no studies have tested genistein alone for age-related cognitive decline. Effects may depend on sex, age, and ethnicity.

Aging and related health concerns: Clinical trials (mostly in postmenopausal women) have shown that genistein treatment results in improved cholesterol, insulin/glucose, HOMA-IR, and homocysteine levels.

Safety: Genistein intake via diet or supplementation at clinically-tested doses is generally regarded as safe with some gastrointestinal effects. However, a US observational study has found that higher urinary genistein levels are associated with higher mortality.

Availability: OTC and in diet (soy). Most supplements include other soy isoflavones.	Dose: 50-54 mg/day of genistein to prevent diabetes	Chemical formula: C ₁₅ H ₁₀ O ₅ MW: 270.24 
Half life: 9 hours	BBB: permeable	
Clinical trials: There is a meta-analysis of 7 RCTs including a total of 670 subjects.	Observational studies: There are 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) β , which has been a promising therapeutic target for cognitive impairment, menopausal symptoms, and premenstrual syndrome (PMS) [1] ([WebMD.com](https://pubmed.ncbi.nlm.nih.gov/16111111/)). It is selective for ER β [1], and not ER α , 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: Soy isoflavone interventions that include genistein have improved a few cognitive functions, but no studies have tested genistein alone for age-related cognitive decline. Benefits may depend on sex, age, and ethnicity.

Types of evidence:

- 1 randomized controlled trial of soy isoflavone treatment in Alzheimer's patients
- 1 double-blind randomized controlled trial of genistein aglycone in Sanfilippo syndrome patients
- 1 observational study
- Numerous laboratory studies

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

Many clinical trials 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.

Sanfilipo syndrome (mucopolysaccharidosis type III) is a rare lysosomal storage disease with four subtypes (A, B, C and D), each caused by the deficiency of a different enzyme involved in the degradation of the glycosaminoglycan heparan sulfate. It is a progressive central nervous system disease with early mild developmental delay followed by the development of a severe behavioral disorder from 3 to 5 years of age, leading to progressive cognitive decline. Motor function, feeding, and swallowing progressively deteriorate at around the age of 10.

In a double-blind randomized controlled trial of 20 children with Sanfilipo syndrome, genistein aglycone treatment (160 mg/kg/day; BONISTEIN, manufactured by DSM Nutritional Products Ltd; packaged by Quay Pharmaceuticals) for 12 months did not lead to clinically meaningful reductions in biomarkers (heparin sulfate) or improvement in neuropsychological outcomes [3]. Cerebral spinal fluid (CSF) heparan sulfate concentration was 5.5% lower with genistein treatment, but this was not statistically significant ($p=0.26$), and CSF heparan sulfate also increased in both groups during the open-label extension phase. No evidence of clinical efficacy was observed. Although reduction of urinary glycosaminoglycans was significantly greater in the genistein group (32.1% lower than placebo after 12 months, $p=0.0495$), there were no significant effects on neurocognition, psychological well-being of individuals or families, or other clinical symptoms including inflammatory cytokine levels or actigraphy. In mouse models of Sanfilipo syndrome, genistein reduced neuroinflammation, lysosomal storage, and heparan sulphate levels while correcting abnormal hyperactive behavior [4].

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 [5].



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 β , where it acts as an agonist with 30-fold greater affinity compared to ER α [1]. ER β is expressed in brain regions important for executive function and memory, and its stimulation can lead to improved cognitive functions in preclinical studies [6]. Genistein exhibits antioxidant properties by increasing antioxidant enzymes and glutathione, reducing free radicals, and inhibiting mitochondrial dysfunction [7]. 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 [8]. Preclinical studies have also reported that genistein reduces the production of A β (through inhibition of BACE1) and directly binds to A β 25-35 fragments to prevent them from forming aggregates [9].

Many preclinical studies have evaluated the effects of genistein. Cognitive benefits from genistein have been observed in a rat model of isoflurane-induced neurotoxicity [10], rat and mouse models of LPS-induced cognitive impairment [11; 12], a mouse model of amnesia induced by scopolamine [13], a rat model of stress [14], a mouse model of chronic sleep deprivation [15], a mouse model of hypoxia-induced amnesia [16], diabetes-induced cognitive decline [17], mice fed a high-fat diet [18], a mouse model of Parkinson's [19], and Alzheimer's models [20; 21; 22]. In these studies, genistein inhibited apoptosis (reduced Bad, Bax, caspase-3) [10; 21], increased anti-apoptotic factors (Bcl-2, Bcl-xL) [10], increased synaptic proteins (synaptophysin, PSD-95)[22], decreased tau phosphorylation [22], upregulated neurotrophic/BDNF signaling (CREB/TrkB/BDNF) [10; 11; 13; 16], increased IGF1 [16], promoted acetylcholine neurotransmission [12; 13], improved glucose metabolism/tolerance [18], lowered inflammatory markers (IL-6, IL-1 β , NF-kB, TNF- α , COX2, iNOS, GFAP) [12; 15; 16; 17; 18], modified gut microbiota such that inflammation was reduced [18], suppressed oxidative stress [13; 16], and increased an antioxidant capacity (activation of Nrf2, increased total antioxidant capacity, SOD, and GSH)[12; 13; 15].

In cell culture models of Huntington's disease, genistein treatment stimulated autophagy and decreased mutant huntingtin levels and the number of aggregates, leading to increased viability of cells [23; 24]. In the more recent study, fibroblasts derived from Huntington's disease patients were used and the same results were seen while no effects were seen in fibroblasts derived from control subjects [23]. The number of huntingtin aggregates were decreased to half at the 30 μ M genistein concentration and down to ~10% or so at the 60 μ M concentration, and to control subjects' level with 100 μ M genistein in patient-derived fibroblasts.



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 [25]. Another study of ovariectomized rats showed that genistein treatment (40 mg/kg) resulted in improvement in spatial memory in young but not aged rats [26].

In preclinical Alzheimer's models including cell cultures, genistein decreases Aβ levels [20] and inhibits neuronal apoptosis induced by Aβ [27].

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

Ageing and related health concerns: Clinical trials (mostly in postmenopausal women) have shown that genistein treatment results in improved cholesterol, insulin/glucose, HOMA-IR, and homocysteine levels.

Types of evidence:

- 6 meta-analyses or systematic reviews of randomized controlled trials
- 7 meta-analyses or systematic reviews of observational studies (on dietary, blood, or urinary levels of genistein)
- 2 double-blind randomized controlled trial
- 3 observational studies examining the association between genistein and mortality
- 1 review of genistein for nonalcoholic fatty liver disease
- Numerous laboratory studies

Lifespan: MIXED; HIGHER URINARY LEVELS CORRELATED WITH HIGHER MORTALITY.

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 [28]. In a study based in the US that included 5,179 people from the National Health and Nutrition Examination Survey, no associations with mortality were found for urinary genistein levels, though higher urinary concentrations of total isoflavones were seen in people who died from cardiovascular disease [29].

In a more recent study of the National Health and Nutrition Examination Survey that included a larger US population (11,497 participants) followed for a longer period (mean follow-up of 5.6 years), the all-cause mortality rate was significantly higher in the highest quartile of normalized urinary genistein levels compared to the lowest quartile (incidence rate ratio, 2.14; 95% CI, 1.76 to 2.60)[30]. The mortality rate



was 9.1 (95% CI, 7.8 to 10.7) deaths per 1000 person-years in the lowest quartile compared to 19.2 (95% CI, 17.1 to 21.5) deaths per 1000 person-years in the highest quartile. Using the Kaplan-Meier analysis, survival was significantly higher in the lowest quartile of normalized urinary genistein levels than in the highest quartile (153 deaths in the lowest quartile and 298 deaths in the highest quartile; $p < 0.0001$). In adjusted models, for every log increase in normalized urinary genistein levels, there was a 9% increase in risk of mortality (HR=1.09; 95% CI, 1.04 to 1.15; $p = 0.001$), and individuals in the highest quartile had a 57% higher risk of mortality compared to individuals in the lowest quartile (HR=1.57; 95% CI, 1.23 to 2.00; $p < 0.0001$). This association between higher urinary genistein levels and increasing mortality was significant with and without adjustment for potential confounders (age, sex, race, BMI, cholesterol, serum CRP, hypertension, diabetes mellitus, smoking, estimated glomerular filtration rate).

This study further analyzed cause-specific mortality. Compared to people at the lowest quartile of urinary genistein levels, the highest quartile had a 67% higher cardiovascular mortality in adjusted models (HR=1.67; 95% CI, 1.04 to 2.68; $p = 0.03$) [30]. When using the Cox proportional hazards model, for every log increase of urinary genistein, there was a 14% increase in risk of cardiovascular disease mortality (HR=1.14; 95% CI, 1.05 to 1.24; $p = 0.002$). However, after adjusting for potential confounders, the relationship between urinary genistein and the risk for cardiovascular disease mortality failed to reach statistical significance (HR=1.11; 95% CI, 0.99 to 1.24; $p = 0.06$).

There was no statistically significant relationship between cancer mortality and urinary genistein levels, with (HR=1.01; 95% CI, 0.89 to 1.14; $p = 0.87$) or without adjustment (HR=1.05, 95% CI, 0.96 to 1.16; $p = 0.28$) for potential confounders [30].

Finally, there was a statistically significant relationship between urinary genistein levels and other-cause mortality in unadjusted and adjusted analyses [30]. Using adjusted data, every log increase in urinary genistein was associated with a 13% increase in risk of other-cause mortality (HR=1.13; 95% CI, 1.05 to 1.23; $p = 0.002$). Similarly, a significantly higher risk of other-cause mortality was observed in participants in the highest compared to the lowest quartile in unadjusted (HR=2.21; 95% CI, 1.59 to 3.06; $p < 0.001$) and adjusted models (HR=1.85; 95% CI, 1.33 to 2.57; $p < 0.0001$).

Because the study described above is an observational study, it was not designed to determine if there is a causal relationship between urinary genistein levels and mortality. Although urinary genistein levels have been positively correlated with dietary genistein intake [31], there are also individual differences in how genistein is metabolized (e.g., enzymatic activity within the intestine, liver, and gut microbiome) that can affect the amount of genistein excreted in the urine [30]. In fact, findings from biomarker



studies (e.g., urinary or plasma genistein levels) are not always consistent with observational studies examining dietary intake of genistein (see findings below for different cancers). It is also possible that there are differences in the potential benefit or harm of genistein by ethnicity, genetics, or sex.

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) [32]. 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 [33]. The highest dose (10 µM/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 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) [34]. Other large meta-analyses of numerous observational studies also showed genistein intake associated with lower risk with odds ratios ranging between 0.81-0.87 [35; 36] while one study found no associations [37]. In a subgroup analysis stratified by population, genistein intake was associated with reduced prostate cancer risk in Asian populations but not in Western populations [35]. Potential mechanisms of protective action include agonist activity of estrogen receptors, antioxidant activity, cell cycle inhibition, anti-angiogenesis, inhibition of TNFα, and induction of apoptosis in prostate cancer cells [38].

A different 2018 meta-analysis of 7 prospective studies (2 from Japan, 5 from Europe) that examined the relationship between circulating levels of isoflavones with prostate cancer risk reported that genistein (and daidzein) concentrations were not associated with prostate cancer risk in Japanese men or in European men [39].

In a randomized controlled trial of middle-aged to older men at risk of recurrence of prostate cancer after radical prostatectomy (n=284), treatment with whole soy protein (19.2 g/day) containing 24 mg of genistein for 18 months resulted in reduced circulating testosterone and sex hormone binding globulin (SHBG) levels, but did not affect serum concentrations of other cancer biomarkers (free testosterone,



estradiol, VEGF, IGF-1, IGFBP-3, IGF-1/IGFBP-3 ratio, soluble Fas, Fas-ligand, and sFas/Fas-ligand ratio)[40]. Soy protein supplementation affected the androgen axis, but the effects on other cancer biomarkers remain to be more closely investigated.

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) [37].

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 [41]. 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 associations are also present in Western populations.

Cardiovascular diseases: POTENTIAL IMPROVEMENT IN CHOLESTEROL LEVELS.

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) [42]. 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 [43].

In a new 2021 meta-analysis of 10 randomized controlled trials in postmenopausal women, genistein treatment (most tested 54 mg/day, other doses ranged from 40-90 mg/day) for 3 to 24 months resulted in a significant decrease in total cholesterol (standardized mean difference, -0.79, 95% CI, -1.39 to -0.20; p=0.009) and a significant increase in HDL cholesterol (+0.44; 95% CI, 0.08 to 0.79; p=0.02), but no significant effects on LDL cholesterol (-0.58; 95% CI, - 1.19 to 0.02; p=0.06)[44]. Genistein was not superior to placebo in lowering triglyceride levels or body mass index (BMI).

In a 2020 meta-analysis of 4 randomized controlled trials (including postmenopausal women, postmenopausal women with metabolic syndrome, and patients with non-alcohol fatty liver disease), genistein treatment (54 mg/day for 3 studies, 250 mg/day for 1 study) for 4-48 weeks did not result in



significant reductions of systolic blood pressure (SBP; -5.32 mmHg; 95% CI, -14.59 to 3.96) or diastolic blood pressure (DBP; -2.06 mmHg; 95% CI, -6.41 to 2.28) compared to the placebo group [45]. However, subgroup analyses suggested that more than 6 months of genistein treatment in metabolic syndrome patients can significantly decrease SBP (-13.73 mmHg; 95% CI, -18.10 to -9.37) and DBP (-5.18 mmHg; 95% CI, -6.62 to -3.74).

Genistein's mechanism of action on lipid metabolism is still unclear but may be attributed, in part, to genistein's regulation of genes involved in cholesterol homeostasis (e.g., upregulation of LXR and ABCG1 and downregulation of HMG-CoA reductase)[44].

Genistein's mechanism of action on cardiovascular health may be attributed to increased nitric oxide synthesis, decreased endothelin-1, decreased soluble vascular cellular adhesion molecule-1, and decreased homocysteine levels (reviewed in [45]). Genistein may also improve vascular endothelial function, endothelial-dependent dilation, and vascular smooth muscle cell tone.

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 [46]. 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) [37]. 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 [47].

In a new 2021 meta-analysis of 10 randomized controlled trials in postmenopausal women, genistein treatment (most used 54 mg/day, other doses ranged from 40-90 mg/day) for 3 to 24 months resulted in a significant decrease in HOMA-IR (standardized mean difference, -0.51; 95% CI, -0.88 to -0.14; $p=0.006$)[44]. In subgroup analyses, HOMA-IR was improved more in women with BMI under 30 kg/m² and in those without metabolic disorders ($p<0.0001$). Fasting blood glucose (-0.41; 95% CI, -0.63 to



-0.19; $p=0.0003$) and fasting blood insulin (-0.32; 95% CI, -0.55 to -0.09; $p=0.007$) were also reduced in women receiving genistein.

In an overview of 4 meta-analyses that examined soy isoflavone and genistein interventions in postmenopausal women, while benefits with soy isoflavones were mixed, treatment with genistein specifically showed significant benefits on fasting insulin, blood glucose, and HOMA-IR compared to the placebo group [48].

In preclinical studies, genistein increased β -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- κ B pathway) [49].

Nonalcoholic fatty liver disease (NAFLD): POTENTIAL BENEFIT.

NAFLD is the leading cause of chronic liver disease and may be due, in part, to metabolic aberrations and higher energy intake seen in metabolic disease like diabetes and obesity that lead to an imbalance between the synthesis/influx of hepatic lipids and their oxidation/export.

In a double-blind randomized controlled trial of 82 patients with NAFLD, treatment with genistein (250 mg/day) for 8 weeks resulted in a lower level of insulin ($p=0.001$) and HOMA-IR ($p=0.041$) compared to the placebo group [50]. Genistein treatment also decreased oxidative stress (measured by MDA; $p=0.004$), pro-inflammatory biomarkers (TNF- α , IL-6; $p=0.045$, $p=0.018$, respectively), waist-to-hip ratio ($p=0.021$), body fat percentage ($p=0.015$), and triglyceride levels ($p=0.018$). However, no significant changes were seen with genistein treatment in BMI, fasting blood glucose, and liver enzymes (ALT and AST). A larger and longer duration study may be warranted.

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 [51]. 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 μ M/L [42].

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 [52]. 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%)[53].

Preclinical studies suggest that genistein may activate ER β in osteoblasts [43]. 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 at clinically-tested doses is generally regarded as safe with some gastrointestinal effects. However, a US observational study has found that higher urinary genistein levels are associated with higher mortality.

Types of evidence:

- 1 meta-analysis based on 7 randomized controlled trials
- 1 double-blind randomized controlled trial of genistein aglycone in Sanfilippo syndrome patients
- 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 [46]. 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 [5; 54; 55; 56]. Adverse events were generally mild [55] and no abnormal lab values were observed [5].

While an observational study cannot prove a causal relationship, a study using the National Health and Nutrition Examination Survey that included 11,497 participants from the US with a mean follow-up of



5.6 years reported that individuals in the highest quartile of urinary genistein levels had a 57% higher risk of mortality compared to individuals in the lowest quartile (HR=1.57; 95% CI, 1.23 to 2.00; $p < 0.0001$) [30]. Individual differences in metabolism and excretion of genistein may play a role. This finding does not prove that higher dietary intake of genistein is associated with higher mortality. There is a growing need for more research examining the long-term effects and safety of genistein interventions.

In a double-blind randomized controlled trial of 20 children with Sanfilippo syndrome, treatment with an ultra-high dose of genistein aglycone (160 mg/kg/day; BONISTEIN, manufactured by DSM Nutritional Products Ltd; packaged by Quay Pharmaceuticals) for 12 months was generally well-tolerated but several children experienced changes in hormone levels and progression into puberty [3]. Development of Tanner stage II breast tissue was observed in 3 male participants (4.3, 7.9 and 7.6 years old), which was not present at baseline. Two male participants showed elevated testosterone levels during the study, one of whom had elevated gonadotropin levels and evidence of progression into puberty at 9.5 years old. One female participant developed biochemical and clinical evidence of progression into puberty at 9.1 years old. All participants had high levels of sex hormone binding globulin (SHBG) at baseline (range 153-653 nmol/L). Six participants had elevated alanine transaminase (ALT) at baseline which did not worsen during the study. A total of 4 participants across both genistein and placebo groups exhibited elevated ALT during the course of the study. Five participants across both genistein and placebo groups showed elevated thyroid stimulating hormone during the study, one of whom had previously been treated for hypothyroidism.

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) [57]. 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.

Drug interactions: Drug interactions with genistein are not well-documented ([Drugs.com](https://www.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) [56; 58; 59]. However, soy isoflavone doses of 100 mg/day for 6 months did not improve cognitive function in Alzheimer's patients [5].

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 [60].

In an *in vivo* and *in vitro* study of new genistein formulations, 5 different formulations of genistein capsules were developed and their disintegration and dissolution properties, flowability of the powder, thermal properties, and stability were evaluated [61]. Compared to commercial products, the final product had superior disintegration and dissolution properties, exhibited enhanced action in human cell lines as well as good pharmacokinetic results in animal models. The maximum concentration *in vivo* was 34% higher than achieved by the commercial genistein product.

Research underway: There are only two clinical trials registered at [ClinicalTrials.gov](#) that are currently ongoing and testing the effects of genistein ([ClinicalTrials.gov](#)). One is in bladder cancer patients to reduce the side effects of intravesical therapy ([NCT01489813](#)) and the other is in COVID-19 patients who have been discharged ([NCT04482595](#)).

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

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

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