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

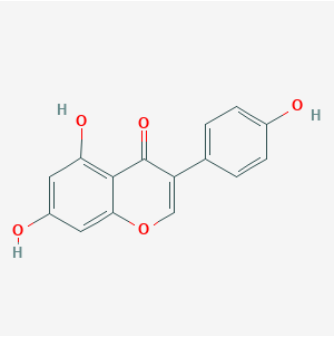
Evidence Summary

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.

Availability: OTC and in diet (soy).	**Dose**: 50-54 mg/day of genistein to prevent diabetes	**Chemical formula:** $C_{15}H_{10}O_5$ **MW**: 270.24  Source: Pubchem
Half life: 9 hours	**BBB**: permeable	
Clinical trials: a meta-analysis of 7 RCTs including a total of 670 subjects	**Observational studies**: 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). It is selective for ERβ [1], and not ERα, 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 ERβ, where it acts as an agonist with 30-fold greater affinity compared to ERα [1]. ERβ 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, TNFα, 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 TNFα, 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 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-kB 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 μM/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 ERβ 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 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)

References:

1. Turner JV, Agatonovic-Kustrin S, Glass BD (2007) Molecular aspects of phytoestrogen selective binding at estrogen receptors. *J Pharm Sci* 96, 1879-1885.https://www.ncbi.nlm.nih.gov/pubmed/17518366

2. Huang MH, Luetters C, Buckwalter GJ *et al.* (2006) Dietary genistein intake and cognitive performance in a multiethnic cohort of midlife women. *Menopause* 13, 621-630.https://www.ncbi.nlm.nih.gov/pubmed/16837884

3. Gleason CE, Fischer BL, Dowling NM *et al.* (2015) Cognitive Effects of Soy Isoflavones in Patients with Alzheimer's Disease. *J Alzheimers Dis* 47, 1009-1019.https://www.ncbi.nlm.nih.gov/pubmed/26401779

4. Zhao L, Brinton RD (2005) Structure-based virtual screening for plant-based ERbeta-selective ligands as potential preventative therapy against age-related neurodegenerative diseases. *J Med Chem* 48, 3463-3466.https://www.ncbi.nlm.nih.gov/pubmed/15887952

5. Sadhukhan P, Saha S, Dutta S *et al.* (2017) Nutraceuticals: An emerging therapeutic approach against the pathogenesis of Alzheimer's disease. *Pharmacol Res.*https://www.ncbi.nlm.nih.gov/pubmed/29183770

6. Seo EJ, Fischer N, Efferth T (2017) Phytochemicals as inhibitors of NF-kappaB for treatment of Alzheimer's disease. *Pharmacol Res.*https://www.ncbi.nlm.nih.gov/pubmed/29179999

7. Jiang T, Wang XQ, Ding C *et al.* (2017) Genistein attenuates isoflurane-induced neurotoxicity and improves impaired spatial learning and memory by regulating cAMP/CREB and BDNF-TrkB-PI3K/Akt signaling. *Korean J Physiol Pharmacol* 21, 579-589.https://www.ncbi.nlm.nih.gov/pubmed/29200900

8. Lee HJ, Lim SM, Ko DB *et al.* (2017) Soyasapogenol B and Genistein Attenuate Lipopolysaccharide-Induced Memory Impairment in Mice by the Modulation of NF-kappaB-Mediated BDNF Expression. *J Agric Food Chem* 65, 6877-6885.https://www.ncbi.nlm.nih.gov/pubmed/28771341

9. Mirahmadi SM, Shahmohammadi A, Rousta AM *et al.* (2017) Soy isoflavone genistein attenuates lipopolysaccharide-induced cognitive impairments in the rat via exerting anti-oxidative and anti-inflammatory effects. *Cytokine.*https://www.ncbi.nlm.nih.gov/pubmed/29102164

10. Rajput MS, Sarkar PD (2017) Modulation of neuro-inflammatory condition, acetylcholinesterase and antioxidant levels by genistein attenuates diabetes associated cognitive decline in mice. *Chem Biol Interact* 268, 93-102.https://www.ncbi.nlm.nih.gov/pubmed/28259689

11. Arbabi E, Hamidi G, Talaei SA *et al.* (2016) Estrogen agonist genistein differentially influences the cognitive and motor disorders in an ovariectomized animal model of Parkinsonism. *Iran J Basic Med Sci* 19, 1285-1290.https://www.ncbi.nlm.nih.gov/pubmed/28096960

12. Bonet-Costa V, Herranz-Perez V, Blanco-Gandia M *et al.* (2016) Clearing Amyloid-beta through PPARgamma/ApoE Activation by Genistein is a Treatment of Experimental Alzheimer's Disease. *J Alzheimers Dis* 51, 701-711.https://www.ncbi.nlm.nih.gov/pubmed/26890773

13. Wang Y, Cai B, Shao J *et al.* (2016) Genistein suppresses the mitochondrial apoptotic pathway in hippocampal neurons in rats with Alzheimer's disease. *Neural Regen Res* 11, 1153-1158.https://www.ncbi.nlm.nih.gov/pubmed/27630702

14. Neese SL, Wang VC, Doerge DR *et al.* (2010) Impact of dietary genistein and aging on executive function in rats. *Neurotoxicol Teratol* 32, 200-211.https://www.ncbi.nlm.nih.gov/pubmed/19945528

15. Alonso A, Gonzalez-Pardo H, Garrido P *et al.* (2010) Acute effects of 17 beta-estradiol and genistein on insulin sensitivity and spatial memory in aged ovariectomized female rats. *Age (Dordr)* 32, 421-434.https://www.ncbi.nlm.nih.gov/pubmed/20467821

16. Zeng H, Chen Q, Zhao B (2004) Genistein ameliorates beta-amyloid peptide (25-35)-induced hippocampal neuronal apoptosis. *Free Radic Biol Med* 36, 180-188.https://www.ncbi.nlm.nih.gov/pubmed/14744630

17. Hozawa A, Sugawara Y, Tomata Y *et al.* (2013) Relationship between serum isoflavone levels and disability-free survival among community-dwelling elderly individuals: nested case-control study of the Tsurugaya project. *J Gerontol A Biol Sci Med Sci* 68, 465-472.https://www.ncbi.nlm.nih.gov/pubmed/23051976

18. Reger MK, Zollinger TW, Liu Z *et al.* (2016) Urinary phytoestrogens and cancer, cardiovascular, and all-cause mortality in the continuous National Health and Nutrition Examination Survey. *Eur J Nutr* 55, 1029-1040.https://www.ncbi.nlm.nih.gov/pubmed/25943648

19. Lee EB, Ahn D, Kim BJ *et al.* (2015) Genistein from Vigna angularis Extends Lifespan in Caenorhabditis elegans. *Biomol Ther (Seoul)* 23, 77-83.https://www.ncbi.nlm.nih.gov/pubmed/25593647

20. Altun D, Uysal H, Askin H *et al.* (2011) Determination of the effects of genistein on the longevity of Drosophila melanogaster meigen (Diptera; Drosophilidae). *Bull Environ Contam Toxicol* 86, 120-123.https://www.ncbi.nlm.nih.gov/pubmed/21127834

21. Applegate CC, Rowles JL, Ranard KM *et al.* (2018) Soy Consumption and the Risk of Prostate Cancer: An Updated Systematic Review and Meta-Analysis. *Nutrients* 10.https://www.ncbi.nlm.nih.gov/pubmed/29300347

22. Zhang Q, Feng H, Qluwakemi B *et al.* (2017) Phytoestrogens and risk of prostate cancer: an updated meta-analysis of epidemiologic studies. *Int J Food Sci Nutr* 68, 28-42.https://www.ncbi.nlm.nih.gov/pubmed/27687296

23. Zhang M, Wang K, Chen L *et al.* (2016) Is phytoestrogen intake associated with decreased risk of prostate cancer? A systematic review of epidemiological studies based on 17,546 cases. *Andrology* 4, 745-756.https://www.ncbi.nlm.nih.gov/pubmed/27260185

24. Rienks J, Barbaresko J, Nothlings U (2017) Association of isoflavone biomarkers with risk of chronic disease and mortality: a systematic review and meta-analysis of observational studies. *Nutr Rev* 75, 616-641.https://www.ncbi.nlm.nih.gov/pubmed/28969363

25. Kyle E, Neckers L, Takimoto C *et al.* (1997) Genistein-induced apoptosis of prostate cancer cells is preceded by a specific decrease in focal adhesion kinase activity. *Mol Pharmacol* 51, 193-200.https://www.ncbi.nlm.nih.gov/pubmed/9203623

26. Ko KP, Yeo Y, Yoon JH *et al.* (2017) Plasma phytoestrogens concentration and risk of colorectal cancer in two different Asian populations. *Clin Nutr.*https://www.ncbi.nlm.nih.gov/pubmed/28778370

27. Li J, Liu Y, Wang T *et al.* (2016) Does genistein lower plasma lipids and homocysteine levels in postmenopausal women? A meta-analysis. *Climacteric* 19, 440-447.https://www.ncbi.nlm.nih.gov/pubmed/27338295

28. North American Menopause S (2011) The role of soy isoflavones in menopausal health: report of The North American Menopause Society/Wulf H. Utian Translational Science Symposium in Chicago, IL (October 2010). *Menopause* 18, 732-753.https://www.ncbi.nlm.nih.gov/pubmed/21685820

29. Liu Y, Li J, Wang T *et al.* (2017) The effect of genistein on glucose control and insulin sensitivity in postmenopausal women: A meta-analysis. *Maturitas* 97, 44-52.https://www.ncbi.nlm.nih.gov/pubmed/28159061

30. Ding M, Pan A, Manson JE *et al.* (2016) Consumption of soy foods and isoflavones and risk of type 2 diabetes: a pooled analysis of three US cohorts. *Eur J Clin Nutr* 70, 1381-1387.https://www.ncbi.nlm.nih.gov/pubmed/27380886

31. Babu PV, Liu D, Gilbert ER (2013) Recent advances in understanding the anti-diabetic actions of dietary flavonoids. *J Nutr Biochem* 24, 1777-1789.https://www.ncbi.nlm.nih.gov/pubmed/24029069

32. Kuo HK, Sorond FA, Chen JH *et al.* (2005) The role of homocysteine in multisystem age-related problems: a systematic review. *J Gerontol A Biol Sci Med Sci* 60, 1190-1201.http://www.ncbi.nlm.nih.gov/pubmed/16183962

33. Abdi F, Alimoradi Z, Haqi P *et al.* (2016) Effects of phytoestrogens on bone mineral density during the menopause transition: a systematic review of randomized, controlled trials. *Climacteric* 19, 535-545.https://www.ncbi.nlm.nih.gov/pubmed/27710141

34. Hernandez G, Zhao L, Franke AA *et al.* (2018) Pharmacokinetics and safety profile of single-dose administration of an estrogen receptor beta-selective phytoestrogenic (phytoSERM) formulation in perimenopausal and postmenopausal women. *Menopause* 25, 191-196.https://www.ncbi.nlm.nih.gov/pubmed/28926513

35. Henderson VW, St John JA, Hodis HN *et al.* (2012) Long-term soy isoflavone supplementation and cognition in women: a randomized, controlled trial. *Neurology* 78, 1841-1848.https://www.ncbi.nlm.nih.gov/pubmed/22665144

36. Gleason CE, Carlsson CM, Barnet JH *et al.* (2009) A preliminary study of the safety, feasibility and cognitive efficacy of soy isoflavone supplements in older men and women. *Age Ageing* 38, 86-93.https://www.ncbi.nlm.nih.gov/pubmed/19054783

37. National Toxicology P (2008) Toxicology and carcinogenesis studies of genistein (Cas No. 446-72-0) in Sprague-Dawley rats (feed study). *Natl Toxicol Program Tech Rep Ser*, 1-240.https://www.ncbi.nlm.nih.gov/pubmed/18685716

38. Duffy R, Wiseman H, File SE (2003) Improved cognitive function in postmenopausal women after 12 weeks of consumption of a soya extract containing isoflavones. *Pharmacol Biochem Behav* 75, 721-729.https://www.ncbi.nlm.nih.gov/pubmed/12895690

39. File SE, Jarrett N, Fluck E *et al.* (2001) Eating soya improves human memory. *Psychopharmacology (Berl)* 157, 430-436.https://www.ncbi.nlm.nih.gov/pubmed/11605103

40. Devi KP, Shanmuganathan B, Manayi A *et al.* (2016) Molecular and Therapeutic Targets of Genistein in Alzheimer's Disease. *Mol Neurobiol.*https://www.ncbi.nlm.nih.gov/pubmed/27796744

Disclaimer: *Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the Terms & Conditions.*

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. To view our official ratings, visit Cognitive Vitality's Rating page.