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.

Soy Isoflavones

Evidence Summary

Soy isoflavones may protect against some cancers, diabetes, cognitive decline, menopausal symptoms, and atherosclerosis; they are generally regarded as safe.

Neuroprotective Benefit: Soy isoflavone interventions may improve a few cognitive functions, though the benefits may depend on sex, age, and ethnicity.

Aging and related health concerns: Soy isoflavone intake may be protective against some cancers, diabetes, menopausal symptoms, and atherosclerosis.

Safety: Soy isoflavone intake via diet or supplementation is regarded as safe with a side effect profile that is similar to what is experienced with placebo.

Availability: OTC supplements and in diet (soy and other legumes)	**Dose:** 60-100 mg of soy isoflavones/day for some cognitive benefits	**Chemical formula:** $C_{15}H_{10}O_4$ (daidzein), $C_{15}H_{10}O_5$ (genistein), $C_{16}H_{12}O_5$ (glycitein) **MW:** 254.23 (daidzein), 270.24 (genistein), 284.26 (glycitein)
Half life: 9, 6, and 3 hours for genistein, daidzein, and glycitein, respectively	**BBB:** permeable	
Clinical trials: 10 meta-analyses of RCTs involving ~10,000 subjects mostly in menopausal women	**Observational studies:** 8 meta-analyses of observational studies including one with over 640,000 people	

What is it? Soy isoflavones include genistein, genistin (glycoside, or sugar-bound form of genistein), dihydrogenistein (metabolite of genistein), daidzein, daidzin (glycoside of daidzein), equol (metabolite of daidzein), glycitein, glycitin (glycoside of glycitein), and dihydroglycitein (metabolite of glycitein). The whole soybean contains approximately equal amounts of genistein and daidzein, with smaller amounts of glycitein.

Soy isoflavones have been studied for preventing high cholesterol and high blood pressure. Because soy isoflavones are able to interact with estrogen receptors, they have also drawn attention for women's health, particularly for prevention of menopausal symptoms (e.g., hot flashes, cognitive symptoms) [1], breast pain, breast cancer, and premenstrual syndrome (PMS)(WebMD.com). Soy isoflavones preferentially interact with estrogen receptor (ER) β, and not ERα, which is associated with the classical effects of estrogen, including promoting breast and reproductive organ cancers [2].

Neuroprotective Benefit: Soy isoflavone interventions may improve a few cognitive functions, though the benefits may depend on sex, age, and ethnicity.

Types of evidence:

- 1 meta-analysis based on 10 placebo-controlled RCTs
- 7 clinical trials testing soy isoflavones, 1 in Alzheimer's patients and the others in postmenopausal women
- Numerous laboratory studies

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

Menopausal women: The clinical literature of soy isoflavones on cognitive function suggests some benefit in women younger than age 65 with little benefit for women over age 65 [1]. This is consistent with a "critical window" hypothesis similar to the benefits of hormone replacement therapy [3].

A 2015 meta-analysis of 10 placebo-controlled randomized controlled trials (a total of 1,024 subjects) reported that soy isoflavone supplementation (ranging from 6 weeks to 30 months) significantly improved summary cognitive function test scores and visual memory [4]. Subgroup analyses showed that statistically significant differences were seen for non-US countries; for mean age younger than 60 years; and for treatment durations under 12 months.

The most recent double-blind randomized controlled trial in 18 postmenopausal women reported that 50 or 100 mg of soy isoflavones (16.7 or 33.3 mg each of genistein, daidzein, and S-equol) resulted in peak plasma concentrations of genistein, daidzein, and S-equol at 9, 6, and 4 hours, respectively [5]. This was a substudy of a larger and longer randomized controlled trial of 71 subjects with outcomes that include cognitive and vasomotor symptoms, the results of which have not been published yet.

A recent large double-blind randomized controlled trial of 350 postmenopausal women reported that treatment with 25 g of isoflavone-rich soy protein (52 mg of genistein, 36 mg of daidzein, and 3 mg glycitein) for 2.5 years did not produce significant differences in global cognition, but did improve visual memory [6]. Post-hoc analyses suggested that women between 5-10 years of menopause were more likely to show cognitive improvement than women 10 years post-menopause. The study reported that isoflavones did not improve performance on other cognitive domains, including executive functions.

A few smaller double-blind randomized controlled trials in postmenopausal women reported that isoflavone treatment (60 mg/day in one study and 110 mg/day in the other) for 4-6 months resulted in improvements in episodic memory [7], attention [7], and category fluency [8]. They found no significant improvements over placebo in nonverbal memory, category generation, planning ability, or rule-learning [7; 8].

Older adults: In a small randomized controlled trial of 30 older men and women, a 6 month treatment with 100 mg/day of soy isoflavones (Novasoy brand; 85% genistein and daidzein) resulted in improved visuospatial memory and construction, verbal fluency, and speeded dexterity [9]. However, isoflavone-

treated subjects performed worse on 2 tests of executive function. This study was small and included 11 cognitive tests with 18 different variables, so it is unclear whether improvements or declines in a few functions occurred by chance.

Young adults: In a small clinical study of 27 young healthy adults (student volunteers), high soy diet (100 mg total of isoflavones/day) for 10 weeks resulted in significant improvements in short-term and long-term memory and in mental flexibility compared to those in the control diet (0.5 mg/day) [10]. High soy diet also improved performance on letter fluency and test of planning in females, but not in males. No effects of isoflavones were seen on tests of attention or a category generation task.

Human research to suggest benefits to patients with dementia:
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 [11]. In fact, both treatment and placebo groups appeared to decline on the Mini Mental State Exam.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
There are numerous potential mechanisms of action for neuroprotection with soy isoflavones. The primary mechanism of action is on ERβ, where soy isoflavones act as agonists [2]. ERβ is expressed in brain regions important for executive function and memory, and its stimulation can lead to improved cognitive functions in preclinical studies [12]. Of soy isoflavones, genistein has the highest affinity for ERβ, followed by daidzien, then glycitein [13].

Only 20-30% of Western adults (compared to 50-60% of Asians) can metabolize daidzein to S-equol using intestinal bacteria [1]. S-equol has higher bioavailability and higher ERβ affinity compared to daidzein, with affinity comparable to that of genistein [13; 14].

Soy isoflavones also exhibit antioxidant, anti-apoptotic, and anti-inflammatory activities [15]. See Genistein report for details of its neuroprotective mechanisms of action.

APOE4 interactions: In a randomized controlled trial of 59 people with Alzheimer's disease, APOE4 genotype (31 were E4 carriers) did not affect the response to soy isoflavone treatment [11].

Aging and related health concerns: Soy isoflavone intake may be protective against some cancers, diabetes, menopausal symptoms, and atherosclerosis.

Types of evidence:

- 9 meta-analyses or systematic reviews based on RCTs
- 8 meta-analyses or systematic reviews based on observational studies
- 1 double-blind RCT
- 1 open-label clinical trial
- 2 observational studies
- Numerous laboratory studies

Lifespan: MIXED/INCONCLUSIVE. In a case-control study of Japanese people aged 70 and older, serum levels of genistein (or daidzein) were not associated with disability or death, but higher serum equol (daidzein metabolite) levels were associated with lower disability/death (OR=0.55, 95% CI, 0.33-0.93) [16]. In contrast, in a study based in the US, higher urinary concentrations of daidzein were associated with *increased* risk of all-cause mortality (HR=1.43, when highest tertile was compared to lowest tertile) [17]. No associations with mortality were found for urinary genistein levels.

Prostate cancer: POTENTIAL BENEFIT. A new 2018 meta-analysis of 30 observational studies in men reported that total soy food (RR=0.71, 95% CI, 0.58-0.85), genistein (RR=0.84, 95% CI, 0.73-0.97), daidzein (RR=0.84, 95% CI, 0.73-0.97), and unfermented soy food (RR=0.65, 95% CI, 0.56-0.83) intakes were significantly associated with a reduced risk of prostate cancer [18]. However, fermented soy food intake, total isoflavone intake, and circulating isoflavone levels were not associated with lowered risk in this study.

A 2017 meta-analysis of 40 observational studies examining isoflavone biomarkers (in plasma, serum, or urine) also reported a significant risk reduction of 19% with higher concentrations of daidzein (OR=0.81, 95% CI, 0.67-0.99) but not genistein (OR=0.84) or equol (OR=0.81) [19]. A different 2017 meta-analysis of 23 observational studies reported that daidzein (OR, 0.85; 95% CI: 0.75–0.96), genistein (OR, 0.87; 95% CI: 0.78–0.98), and glycitein (OR, 0.89; 95% CI: 0.81–0.98) were associated with a reduction of prostate cancer risk, but total isoflavones (OR, 0.93; 95% CI: 0.84–1.04) and equol (OR, 0.86; 95% CI: 0.66–1.14) were not [20]. A 2016 systematic review involving 29 epidemiological studies with 17,546 subjects reported that the pooled OR for soy isoflavone intake was 0.77 (95% CI, 0.66-0.88) [21]. A subgroup analysis showed that associations were significant among Asians and Caucasians but not among Africans. This may be a reflection of the number of studies carried out in different populations

as there are overwhelmingly more studies in Asians, and the studies in other populations may be underpowered.

Soy isoflavone may have protective properties due to their agonist activity of estrogen receptors, antioxidant activity, cell cycle inhibition, anti-angiogenesis, inhibition of TNFα, and induction of apoptosis in prostate cancer cells [22].

Breast cancer: POTENTIAL BENEFIT. A 2017 meta-analysis of 40 observational studies examining isoflavone biomarkers (in plasma, serum, or urine) reported that higher daidzein and genistein concentrations were associated with a 34% and 28% lower risk of breast cancer, respectively [19]. Another 2017 meta-analysis involving 16 cohort studies with 648,913 subjects reported that high dietary intake of soy foods was associated with a significantly lower breast cancer risk, though the full text of this study was not accessible [23].

Human trials have shown that soy products do not increase circulating estradiol levels or affect estrogen-responsive target tissues [24]. Prospective data of soy use in women taking tamoxifen (treatment for breast cancer) have not indicated increased risk of recurrence. However, better long-term controlled studies confirming safety is required before high dose (over 100 mg/day) isoflavones can be recommended for breast cancer patients.

Colorectal cancer: POTENTIAL BENEFIT. A 2016 systematic review of 17 epidemiological studies reported that higher soy isoflavone consumption was associated with reduced colorectal cancer risk by 22% (RR=0.78, 95% CI, 0.72-0.85) [25]. A subgroup analysis showed that a protective effect was observed with soy foods/products (RR=0.79, 95% CI, 0.69-0.89) and in Asian populations (RR=0.79, 95% CI, 0.72-0.87). It is unclear whether these preventive benefits also occur in Western populations.

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]. In the Korean population, no associations were found with daidzein, while in the Vietnamese population, genistein, daidzein, and total isoflavones were associated with decreased risks of colorectal cancer (OR=0.43, 95% CI, 0.25–0.73 for genistein; OR=0.48, 95% CI, 0.28–0.82 for daidzein; and OR=0.39, 95% CI, 0.23–0.67 for total isoflavones).

Cardiovascular: BENEFIT. A meta-analysis of 10 randomized controlled trials (973 subjects total) reported that soy isoflavone treatment resulted in a significant reduction in plasma total cholesterol (-

7.38 mg/dL; 95% CI, -13.84 to -0.92) and LDL (-6.25 mg/dL; 95% CI, -12.39 to -0.10) concentrations, whereas plasma levels of HDL (0.97 mg/dL; 95% CI, -0.69 to 2.63) and triglycerides (-6.74 mg/dL; 95% CI: -15.36 to 1.89) remained unaffected [27].
A meta-analysis of 11 randomized controlled trials reported that soy isoflavone treatments (65-153 mg/day) did not lead to a significant reduction in blood pressure in normotensive subjects but reduced systolic blood pressure by 5.94 mmHg (95% CI, -10.55 to -1.34 mmHg) and diastolic blood pressure by 3.35 mmHg (95% CI, -6.52 to -0.19 mmHg) in hypertensive subjects [28].

Diabetes: BENEFIT. In a meta-analysis of 17 randomized controlled trials in menopausal women (1,529 women total), treatment with soy isoflavones for 3-36 months significantly reduced fasting blood glucose levels (by -0.22 mmol/L; 95% CI: -0.38 to -0.07 mmol/L), insulin levels (by -0.43 µIU/mL; 95% CI: -0.71 to -0.14 µIU/mL), and HOMA-IR, a marker of insulin resistance (by -0.52; 95% CI: -0.76 to -0.28) compared to placebo groups [29]. This study suggested that of the different isoflavones, genistein alone may have played an important role in improving glucose metabolism.

A 2017 meta-analysis of 40 observational studies examining isoflavone biomarkers (in plasma, serum, or urine) in men and women reported that higher daidzein and genistein concentrations were associated with a 19% and 21% decreased risk for diabetes (OR=0.81, 95% CI, 0.66-0.99 for daidzein; OR=0.79, 95% CI, 0.62-0.99 for genistein) [19]. Total isoflavones did not reach statistical significance (OR=0.90, 95% CI, 0.72-1.13).

A 2016 meta-analysis of 3 observational studies including 163,457 people reported an 11% decreased risk for diabetes (HR=0.89, 95% CI, 0.83-0.93) when comparing the highest quintile versus the lowest of soy isoflavones [30]. The HR was 0.91 (95% CI, 0.85-0.98) for genistein and 0.87 (95% CI, 0.81-0.94) for daidzein.

In preclinical studies, soy isoflavones increased β-cell mass and proliferation, increased insulin secretion and glucose tolerance, improved glucose homeostasis, and decreased hyperglycemia by activation of several pathways (cAMP-PKA-dependent ERK1/2 signaling pathway, CAMKII and calcium signaling, decreased NF-kB pathway) [31].
Osteoporosis: MIXED/POTENTIAL BENEFIT. A systematic review of 23 double-blind randomized controlled trials has reported potentially protective benefits of soy isoflavone supplementation, though the data were mixed [32]. Study design may have been an issue for many of these studies, as efficacy studies need to be performed for a minimum of 24 months, and only 4 out of 23 were designed this way [1].

Preclinical studies suggest that soy isoflavones activate ERβ in osteoblasts, inhibit cell growth, and prevent osteoclast activity [1]. Soy isoflavones may prevent osteoporosis by suppressing bone resorption and minimizing bone loss.

Homocysteine: MIXED. High 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 [33]. A meta-analysis of 18 randomized controlled trials testing soy or soy isoflavone treatments reported that these interventions did not have any effects on homocysteine levels [34]. However, 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 [35].

Menopausal symptoms: BENEFIT. A 2015 meta-analysis of 15 randomized controlled trials in menopausal women reported that isoflavone treatments (mostly of soy, a few with red clover, and one on equol; doses ranging from 25-100 mg/day) significantly reduced daily hot flash frequency compared to placebo (mean difference, -0.89)[36]. An older meta-analysis of 19 trials in menopausal women reported that treatment with extracted or synthesized soybean isoflavones (for 6 weeks to 12 months) significantly reduced the frequency of hot flashes by 20.6% (95% CI, -28.38 to -12.86) and severity of hot flashes by 26.2% (95% CI, -42.23 to -10.15) compared to placebo [37]. Isoflavone supplements providing more than 18.8 mg of genistein were more than twice as potent at reducing hot flash frequency compared to lower genistein supplements.

In 2011, the North American Menopause Society stated that initial treatment with isoflavones is reasonable in postmenopausal women with distressing vasomotor symptoms [1]. The recommended starting isoflavone dose should be 50 mg/day or higher, and therapy should be given for at least 12 weeks. If responsive to supplementation, treatment can continue while monitoring side effects, but if unresponsive after 12 weeks, other treatment options should be pursued.

Safety: Soy isoflavone intake via diet or supplementation is regarded as safe with a side effect profile that is similar to what is experienced with placebo.

Types of evidence:

- 3 meta-analyses based on 7, 10, and 15 randomized controlled trials
- 1 systematic review based on 131 studies (40 RCTs, 11 uncontrolled, 80 observational)
- 4 randomized controlled trials

A 2015 meta-analysis of 10 randomized controlled trials including 1,024 menopausal women reported that no statistically significant differences were seen between soy isoflavone supplementation and placebo [4]. Two of the randomized controlled trials reported gastrointestinal and musculoskeletal complaints. Another 2015 meta-analysis of 15 randomized controlled trials with menopausal women also concluded that the number of side effects are not significantly different between soy isoflavone and placebo groups [36]. There was one trial where the placebo group experienced significantly more side effects than those in the soy/phytoestrogen group.

Individual randomized controlled trials, including one in Alzheimer's patients, reported good safety profiles with soy isoflavone interventions [5; 6; 9; 11]. Adverse events were generally mild [6] and no abnormal lab values were observed [11].

One systematic review of 131 studies (40 RCTs, 11 uncontrolled, 80 observational) in patients with or at risk of breast cancer suggested that while there is no clear evidence of harm, better evidence confirming safety is required before use of high dose (over 100 mg/day) isoflavones can be recommended for breast cancer patients [24].

Treato.com rates soy isoflavones 4.1 stars out of 5. As of January 19, 2018, there have been 149 concerns from 20,525 posts, 253 of which were for weight loss, 147 for weight gain, 63 for blood clots, 43 for bone loss, and 33 for aggression.

Drug interactions: Drug interactions with soy isoflavones are not well-documented (Drugs.com). Because they bind to estrogen receptors, they will likely interact with drugs that target the estrogen system.

Sources and dosing: Soy isoflavones 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. Roasting and fermentation appear to increase the content of aglycones (genistein, daidzein, and glycitein) relative to the sugar bound glycosides (genistin, daidzin, and glycitin)(Examine.com). Doses that showed improvement in some cognitive domains in clinical studies ranged from 60-100 mg of soy isoflavones/day [7; 9; 10]. However, soy isoflavone doses of 100 mg/day for 6 months did not improve cognitive function in Alzheimer's patients [11].

Research underway: There are 6 ongoing clinical trials testing soy isoflavones, two in preventing or treating breast cancer (NCT00204490, NCT01219075), two in prostate cancer (treatment and prevention of recurrence)(NCT01682941, NCT01036321), one in lung cancer (NCT01958372), and one in head/neck cancer (NCT02075112).

Search terms:

Pubmed, Google: Soy isoflavones

- + 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
- Examine.com
- Treato.com
- Drugs.com
- WebMD.com
- Labdoor.com (0)
- ConsumerLab.com
- Patientslikeme

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