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

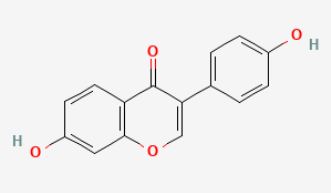
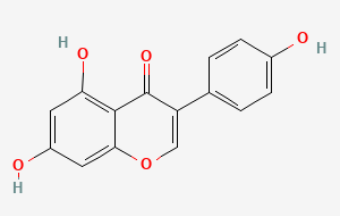
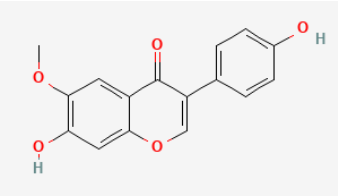
Evidence Summary

Soy isoflavones may protect against some cancers, cardiovascular diseases, diabetes, cognitive decline, osteoporosis, and menopausal symptoms. Soy isoflavones are generally regarded as safe.

Neuroprotective Benefit: Clinical trials have shown that soy isoflavone interventions improve some cognitive domains, though the extent of improvement likely depends on many factors such as age, ethnicity, treatment formulation, and duration.

Aging and related health concerns: Higher intake of soy isoflavones is associated with lower risks of mortality, cardiovascular diseases, some cancers, type 2 diabetes, and osteoporosis. Soy isoflavones also alleviate some menopausal symptoms.

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. Soy isoflavone treatment does not alter levels of hormones such as testosterone and estradiol.

Availability: OTC supplements and in diet (soy and other legumes)	**Dose**: 60-100 mg of soy isoflavones/day, orally, for some cognitive benefits	**Chemical formula**: Daidzein: $C_{15}H_{10}O_4$  Source: PubChem Genistein: $C_{15}H_{10}O_5$  Source: PubChem Glycitein: $C_{16}H_{12}O_5$  Source: PubChem **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: Numerous meta-analyses of clinical trials have been carried out, many of which including over a thousand people.	**Observational studies**: Numerous meta-analyses of observational studies have been carried out, including one with over 700,000 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 are one of the main classes of phytoestrogens, and they are able to interact with estrogen receptors, thus drawing 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). Other classes of phytoestrogens include lignans, which are rich in grains, nuts, seeds, and teas; and coumarins, which are present in coffee, nuts, wine, and tea. While an estrogen-based hormone replacement therapy is effective in reducing hot flashes and cognitive symptoms of menopause, it can elevate risks for stroke, heart attack, breast cancer, and other conditions [2; 3]. 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 [4]. Selective activation of ERβ by soy isoflavones may promote estrogen-mediated neuronal plasticity and memory function without these peripheral adverse effects [5]. This possibility is being tested in a clinical trial of peri/post-menopausal women (NCT05664477).

Soy isoflavones have also been studied for preventing or treating high cholesterol, high blood pressure, type 2 diabetes, and other metabolic disorders.

Neuroprotective Benefit: Clinical trials have shown that soy isoflavone interventions improve some cognitive domains, though the extent of improvement likely depends on many factors such as age, ethnicity, treatment formulation, and duration.

Types of evidence:

- 2 meta-analyses of randomized controlled trials
- 10 clinical trials testing soy isoflavones, 1 in Alzheimer's patients and the others in peri/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, while the benefits for women over age 65 are less clear [1]. This is consistent with a "critical window" hypothesis similar to the benefits of hormone replacement therapy [6].

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 [7]. 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.

In a more recent 2020 meta-analysis of 16 randomized controlled trials including a total of 1,386 participants (1,252 of whom were postmenopausal women), treatment with soy isoflavones (60 to 160 mg/day, orally) for 6-130 weeks improved overall cognitive function (standardized mean difference [SMD]=0.19; 95% CI, 0.07 to 0.32) and memory (SMD=0.15; 95% CI, 0.03 to 0.26) [8].

Other cognitive domains (executive function, psychomotor speed, attention/working memory, language, visuospatial reasoning) were not significantly improved by soy isoflavones. Of the 16 trials, 2 were conducted in Asian countries and 14 were conducted in non-Asian countries. Subgroup analysis did not show a statistically significant difference in the effects of soy isoflavones by duration of intervention (<6 vs ≥6 months), dose (<100 vs ≥100 mg/d), age (<60 vs ≥60 years old), region (Asia vs others), or study population (postmenopausal vs others), after Bonferroni correction. However, high-dose trials showed numerically better results than low-dose trials, and younger individuals appeared to gain more cognitive benefits from soy isoflavones than older individuals.

A 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 [9]. 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 [10], attention [10], and category fluency [11]. They found no significant improvements over placebo in nonverbal memory, category generation, planning ability, or rule-learning [10; 11].

A 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 [12]. This was a substudy of a larger and longer randomized controlled trial of 71 cognitively unimpaired peri-menopausal women (age 45-60) with at least one cognitive complaint and one vasomotor-related symptom. In this phase 1b/2a double-blind randomized controlled trial, treatment with soy isoflavones (PhytoSERM; 50 and 100 mg/day, orally; 16.7 or 33.3 mg each of genistein, daidzein, and S-equol) for 12 weeks did not result in statistically significant differences in neuropsychological composite score compared to placebo [13]. These findings were expected, given the primary objective of this study was to test safety, tolerability, and feasibility, and the study was underpowered to detect statistically significant cognitive effects.

In a retrospective responder analysis of the same phase 1b/2a study, soy isoflavone treatment (PhytoSERM; 50 mg/day or 100 mg/day; 16.7 or 33.3 mg/day each of genistein, daidzein, and S-equol, orally) did not show significant improvement in various cognitive functions assessed compared to placebo [5]. However, treatment with the 50 mg dose of PhytoSERM resulted in a significant enhancement in executive function, measured by the Trails making B test, compared to their own baseline, whereas no significant effects were seen in the placebo or with the 100 mg dose of PhytoSERM. Performance on the Trails making B test was not modulated by mitochondrial haplotypes or APOE genotype. Neither 50 mg/day nor 100 mg/day of PhytoSERM improved immediate recall, delayed recall, or recognition on the Rey auditory verbal learning test (RAVLT), nor did genetic variation (by mitochondrial haplotype H vs non-H, and by APOE4 genotype) modulate any of these outcomes. But mitochondrial haplogroup H receiving placebo had a significantly decreased 677777"learning over trials" parameter of the RAVLT compared to non-H haplogroups, whereas the 50 mg/day PhytoSERM treatment prevented this decline (-1 vs -10; p=0.048). The mitochondrial haplogroup H has a higher risk of late-onset Alzheimer's disease [14]. This preventative effect was not observed in non-H haplogroups [5]. PhytoSERM treatment also did not significantly affect episodic memory (measured by immediate and delayed paragraph recall from the Wechsler Memory Scale-Revised) or global cognition (measured by the MMSE) throughout the trial. Due to the sample size, statistical power was not adequate to

account for the multiple comparisons. A larger study is underway testing the effects of PhytoSERM in preventing menopause-associated decline in brain metabolism (measured by FDG-PET) in peri- and post-menopausal women (NCT05664477).

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 [15]. 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.

In a small randomized controlled crossover trial of 23 healthy older men and women, unsalted soy nuts (67 g/day) that provided 174 mg of soy isoflavones per day for 16 weeks increased regional cerebral blood flow in 4 brain clusters located in the left occipital and temporal lobes, bilateral occipital lobe, right occipital and parietal lobes, and left frontal lobe, after family-wise error correction [16]. These 4 regions are involved in psychomotor speed performance and this function was improved with the soy nut intervention (by 20 ± 37 ms; from 295 ± 68 ms after the control period to 275 ± 49 ms after the soy nut intervention; p=0.005). The authors suggested that these effects on cerebral blood flow may be mediated in part by the increase in nitric oxide bioavailability in the endothelium, as observed with other classes of flavonoids (reviewed in [17]). Soy nuts/isoflavones did not significantly improve executive function (measured by multitasking test and spatial span test) or memory (measured by delayed matching to sample and paired associates learning tests), or increase global or gray matter cerebral blood flow [16]. The changes in cerebral blood flow were not accompanied by changes in glucose metabolism. It is also worth noting that the participants could not be blinded to the treatment condition (soy nuts versus no soy nuts), so placebo effects cannot be ruled out (though researchers analyzing the data were blinded).

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) [18]. 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 [19]. 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 [4]. ERβ is expressed in brain regions important for executive function and memory, and its stimulation can lead to improved cognitive functions in preclinical studies [20]. Of soy isoflavones, genistein has the highest affinity for ERβ, followed by daidzien, then glycitein [21].

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 [21; 22].

Soy isoflavones also exhibit antioxidant, anti-apoptotic, and anti-inflammatory activities [23]. See the Genistein report and S-equol report for neuroprotective mechanisms and findings specific to each isoflavone.

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 [19].

Aging and related health concerns: Higher intake of soy isoflavones is associated with lower risks of mortality, cardiovascular diseases, some cancers, type 2 diabetes, and osteoporosis. Soy isoflavones also alleviate some menopausal symptoms.

Types of evidence:

- 19 meta-analyses or systematic reviews based on RCTs
- 14 meta-analyses or systematic reviews based on observational studies

- 1 double-blind RCT
- 1 open-label clinical trial
- 3 observational studies
- Numerous laboratory studies

Lifespan: ASSOCIATED WITH LOWER MORTALITY
In a 2019 meta-analysis of 5 prospective studies including a total of 51,270 participants who were followed up for 2.5-12.5 years, people in the highest category of dietary soy isoflavone intake had a 10% lower risk of all-cause mortality compared with those in the lowest category (pooled effect size=0.90; 95% CI, 0.82 to 0.98; p=0.02)[24]. The same relationship was found in a subgroup analysis of studies with under 10 years of follow-up and of studies that considered energy intake or BMI as a covariate in their analyses. However, a dose-response meta-analysis did not show a significant association between a 10 mg/day increase in dietary soy isoflavone intake and all-cause mortality (pooled effect size=0.98; 95% CI, 0.94 to 1.01; p=0.17).

In 2 prospective cohort studies in the US (Nurses' Health Study and Health Professionals Follow-up Study) that included 75,981 females and 44,001 males who were followed for over 30 years, higher dietary phytoestrogen intake was associated with lower risks of total mortality, cardiovascular mortality, and non-cardiovascular/non-cancer mortality, after multivariable adjustment [25]. Comparing the highest and lowest quintiles, the pooled HRs were 0.89 (95% CI, 0.87 to 0.92) for total mortality, 0.90 (95% CI, 0.85 to 0.96) for cardiovascular mortality, and 0.86 (95% CI, 0.82 to 0.90) for non-cardiovascular/non-cancer mortality. Of phytoestrogens, the pooled HRs (comparing the highest vs lowest quintiles) for isoflavones were 0.90 (95% CI, 0.87 to 0.92) for total mortality, 0.90 (95% CI, 0.84 to 0.95) for cardiovascular mortality, and 0.88 (95% CI, 0.84 to 0.92) for non-cardiovascular/non-cancer mortality.

Higher intakes of individual isoflavones (genistein, daidzein, and glycitein) were also associated with lower risks of total mortality, cardiovascular mortality, and non-cardiovascular/non-cancer mortality [25]. Further analysis of food items (tofu, soy milk, etc.) also showed an association between higher intake and lower total mortality. For example, compared with participants who consumed less than 1 serving/month of tofu or soy milk, the participants who consumed 1 or more serving/week of tofu or soy milk had a 15%-16% lower risk of total mortality. Higher intake of tofu was also associated with lower cardiovascular mortality. It is worth noting that these are observational studies, and they are not designed to determine cause versus effect. For example, people who consumed higher isoflavones (as well as total phytoestrogens) were more likely to be physically active and had a higher modified

alternative healthy eating index (AHEI) score, which could have contributed to their lower overall and cause-specific mortalities. However, some of these variables, including age, BMI, physical activity, smoking status, alcohol intake, and intake of animal-based foods, were statistically controlled for and the significant associations between total phytoestrogens and total mortality persisted.

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) [26]. 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) [27]. No associations with mortality were found for urinary genistein levels.

CANCERS: ASSOCIATED WITH LOWER RISK

In a 2022 meta-analysis of 81 prospective cohort studies including a total of 4.15 million participants (in Asia, US, and Europe), a higher intake of soy isoflavones was significantly associated with a lower risk of cancer incidence (RR=0.94; 95% CI, 0.89 to 0.99), and the risk of overall cancer incidence was reduced by 4% with each 10 mg/day increment of soy isoflavones intake (RR=0.96; 95% CI, 0.94 to 0.99)[28]. However, higher intake of soy isoflavones was not associated with lower cancer mortality (RR=1.00; 95% CI, 0.99 to 1.01).

In a 2019 meta-analysis of 7 prospective studies including a total of 16,683 participants, those with the highest dietary soy isoflavones intake had a 20% lower risk of cancer mortality compared with those in the bottom category (pooled effect size=0.80; 95% CI, 0.67 to 0.94; p=0.008)[24]. A 10 mg/day increase in dietary soy isoflavone intake was associated with a 7% lower risk of mortality from all cancers (pooled effect size=0.93; 95% CI, 0.89 to 0.98; p=0.003). In subgroup analyses, higher dietary soy isoflavone intake was associated with lower cancer mortality in studies conducted in Asian countries, those with under 10 years of follow-up, studies that considered BMI as a confounder, and those that created the models without any adjustment for the energy intake.

In 2 prospective cohort studies in the US (Nurses' Health Study and Health Professionals Follow-up Study) that included 75,981 females and 44,001 males who were followed for over 30 years, higher dietary phytoestrogen intake was not associated with cancer mortality (HR=0.97; 95% CI, 0.92 to 1.03)[25].

Soy isoflavones likely exert protective effects against cancer by promoting antioxidant effects and reducing inflammation [29; 30].

Prostate cancer: ASSOCIATED WITH LOWER RISK
A 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 [31]. 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) [32]. 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 [33]. 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) [34]. 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 [35].

Breast cancer: MAY DECREASE RISK
A 2021 meta-analysis of 18 randomized controlled trials in pre- and/or post-menopausal women reported that treatment with soy isoflavones (36.5-235 mg/day) from soy food or soy supplements for 1-36 months did not significantly alter breast density compared to control/placebo treatment [36].

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 [32]. 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 unavailable [37].

A 2023 meta-analysis of 15 cohort studies and 34 case-control studies examined the relationship between dietary patterns and breast cancer risk, of which 4 cohort studies and 5 case-control studies analyzed intake of soy isoflavones [38]. The meta-analysis found that high soy protein and soy isoflavone intake was associated with a 35% and 32% lower breast cancer risk, respectively (soy protein, RR=0.65; 95% CI, 0.51 to 0.83; soy isoflavone, RR=0.68; 95% CI, 0.55 to 0.82). In the cohort studies, the relative risk of breast cancer with high soy isoflavone intake was 0.85 (95% CI, 0.73 to 0.99). In the case-control studies, the relative risk of breast cancer with high soy isoflavone intake was 0.54 (95% CI, 0.43 to 0.68).

In a 2022 meta-analysis of 7 prospective observational studies, the proportion of women diagnosed with breast cancer was significantly higher in those consumed 0-15 mg/day of soy isoflavones in their diet (75%; $p<0.000001$) when compared to the group that consumed more than 15 mg/day of soy isoflavones (25%)[39]. This association was present in both premenopausal women and postmenopausal women.

In a 2019 meta-analysis of 6 prospective studies including a total of 16,239 participants who were followed up for 2.5-12.5 years, a significant association was found between higher dietary soy isoflavone intake and lower mortality caused by breast cancer (pooled effect size=0.83; 95% CI, 0.69 to 0.99; $p=0.04$)[24]. A 10 mg/day increase in dietary soy isoflavone intake was associated with a 9% lower risk of mortality from breast cancer (pooled effect size=0.91; 95% CI, 0.84 to 0.99; $p=0.02$)). Dietary intake of soy isoflavones was inversely related to death from breast cancer among women with ER-negative breast cancer (pooled effect size=0.77; 95% CI, 0.60 to 0.99; $p=0.04$), but not in those with ER-positive breast cancer (pooled effect size=0.82; 95% CI, 0.59 to 1.12; $p=0.10$).

Human trials have shown that soy products do not increase circulating estradiol levels or affect estrogen-responsive reproductive tissues/organs [40]. In a 2021 meta-analysis of randomized controlled trials, treatment with soy isoflavones (36.5-235 mg/day; from soy food or soy supplements) for 1-36 months did not significantly affect the amount of active estradiol or estrogen homeostasis in premenopausal women (E1 and E2 levels, along with estrogen precursors E1S, androstenedione, progesterone, DHEA, and DHEAS remained unchanged) [36]. Similarly, in postmenopausal women, soy isoflavone treatment did not significantly alter estrogen homeostasis (E2, progesterone, FSH, LH, SHBG, and SHBG/E2 remained unchanged). There were also no significant differences between soy isoflavone

treatment versus control/placebo in breast density, growth factors, cytological classification of mammary epithelial cells, or components of nipple aspiration fluid.

In a 2023 meta-analysis of observational studies in people with breast cancer, higher dietary intake of soy isoflavones was associated with a 26% lower risk of breast cancer recurrence (HR=0.74; 95% CI, 0.60 to 0.92), particularly in postmenopausal women (HR=0.72; 95% CI, 0.55-0.94) and in estrogen receptor-positive survivors (HR=0.82; 95% CI, 0.70 to 0.97), with the greatest risk reduction at 60 mg/day [41].

Anticarcinogenic effects of soy isoflavones may be mediated in part by genistein through a number of molecular pathways, including inhibition of angiogenesis through regulation of VEGF, MMPs, EGFR expressions and NFkB, PI3K/Akt, ERK1/2 signaling pathways (reviewed in [42]).

Colorectal cancer: ASSOCIATED WITH LOWER RISK
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) [43]. 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 [44]. 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).

Gastric cancer: MIXED
In a 2021 meta-analysis of 10 cohort studies and 21 case-control studies including a total of 916,354 participants, soy isoflavone intake was not significantly associated with a lower risk of gastric cancer (RR=0.92; 95% CI, 0.79 to 1.07), but total soybean intake was associated with a 36% lower risk (RR=0.64; 95% CI, 0.51 to 0.80)[45]. In the same meta-analysis, high intake of fermented soybean products was associated with a higher risk of gastric cancer (RR=1.19; 95% CI, 1.02 to 1.38).

Lung cancer: ASSOCIATED WITH LOWER RISK
In a 2022 meta-analysis of 81 prospective cohort studies including a total of 4.15 million participants (in Asia, US, and Europe), a higher intake of soy isoflavones was significantly associated with a lower risk of lung cancer incidence (RR=0.85; 95% CI, 0.72 to 0.99) when comparing the highest and the lowest intake [28].

Cardiovascular diseases: ASSOCIATED WITH LOWER RISK
In a 2023 meta-analysis of 12 observational studies including a total of 701,106 participants, higher dietary soy isoflavone intake was associated with a lower risk of overall cardiovascular diseases (pooled relative risk [RR]=0.91; 95% CI, 0.84 to 0.98) and a lower risk of coronary heart disease [46]. Comparing the highest and lowest intakes of dietary isoflavones, the summary RR for cardiovascular disease risk was 0.96 (95% CI, 0.89 to 1.03). A 3 mg/day increase in dietary soy isoflavone intake was associated with a 16% lower risk of overall cardiovascular diseases among Western people. In Asian people, there were no significant associations between each 10 mg/day increase in dietary soy isoflavone intake and cardiovascular disease risk. In a meta-analysis of 8 observational studies including a total of 477,831 people, the relative risk of coronary heart disease in the highest versus lowest dietary intake of soy isoflavones was 0.92 (95% CI, 0.85 to 0.99). In Western populations, the relative risk was 0.89 (95% CI, 0.83 to 0.96). For every 3 mg/day increase in dietary soy isoflavone intake, the relative risk of coronary heart disease was 0.86 (95% CI, 0.78 to 0.96) in the Western population. In Asian people, there was no significant association between each 10 mg/day increase in dietary soy isoflavone intake and coronary heart disease risk. In a meta-analysis of 6 observational studies with 267,402 people, there was no significant association between soy isoflavone intake and cardiovascular mortality (RR=0.98; 95% CI, 0.92 to 1.04). In a meta-analysis of 5 observational studies with 260,391 people, there was no significant association between dietary soy isoflavone intake and stroke risk (RR=1.08; 95% CI, 0.96 to 1.21).

In a 2019 meta-analysis of 4 prospective studies including a total of 132,913 participants who were followed up for 2.5-12.5 years, no significant association was found between higher dietary soy isoflavone intake and cardiovascular disease mortality (pooled effect size=0.98; 95% CI, 0.90 to 1.06) [24]. A linear dose–response analysis revealed no significant association between an increase of 10 mg/day in dietary intake of soy isoflavones and cardiovascular disease mortality.

In 2 prospective cohort studies in the US (Nurses' Health Study and Health Professionals Follow-up Study) that included 75,981 females and 44,001 males who were followed for over 30 years, higher dietary phytoestrogen intake was associated with lower risks of cardiovascular mortality, after multivariable adjustment [25]. Comparing the highest and lowest quintiles, the pooled HR was 0.90 (95%

CI, 0.85 to 0.96) for cardiovascular mortality. Of phytoestrogens, the pooled HR (comparing the highest vs lowest quintiles) for isoflavones was 0.90 (95% CI, 0.84 to 0.95) for cardiovascular mortality.

Arterial stiffness, which reflects the loss of arterial elasticity, is characterized by age-related changes in the arterial wall structure, including fragmentation of elastin fibers and increased deposition of collagen [47]. The stiffening of arteries is associated with cardiovascular diseases, such as coronary heart disease, stroke, hypertension, heart failure, and others. Pulse-wave velocity (PWV) is a measurement of the velocity at which blood pressure pulse moves through the arteries, and is a biomarker of arterial stiffness. Cardio-ankle vascular index (CAVI) is a measurement that reflects the stiffness of the ascending aorta to the ankle arteries. Systemic arterial compliance (SAC) is a measurement of the relationship between carotid artery pressure and volume of outflow into the aorta. In a 2021 meta-analysis of 8 randomized controlled trials of 276 women and 209 men (with different conditions, including menopause, obesity, cardiometabolic risk factors), soy isoflavone treatment (10 to 85 mg daily) for up to 12 weeks significantly reduced arterial stiffness compared to placebo (standardized mean difference [SMD]=-0.33; 95% CI, -0.47 to -0.19)[48]. Statistically significant effects were observed for PWV (SMD=−0.38; 95% CI, −0.71 to −0.05), SAC (SMD=−0.29; 95% CI, −0.49 to −0.10), and CAVI (SMD=−0.43; 95% CI, −0.83 to −0.02). Subgroup analyses did not show significant differences depending on intervention duration (under 6 weeks vs at or above 6 weeks) or sex.

Postmenopausal women are at higher risk of endothelial dysfunction, which precedes many cardiovascular diseases. In a 2020 meta-analysis of 5 randomized controlled trials of postmenopausal women, treatment with soy products containing isoflavones (49.3 mg to 118 mg/day) for 4 weeks to 2.5 years did not significantly enhance flow-mediated dilation (a measure of vascular function), though subgroup analyses showed that soy protein supplementation had a significant effect (+3.39%; 95% CI, 0.733 to 6.01; p=0.01)[49]. Additional high-quality large randomized controlled trials are needed to validate these findings, particularly as they relate to the specific effects of soy isoflavones.

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 [50].

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 [51].

Protective benefits of phytoestrogens including isoflavones may be mediated through ERβ activation and subsequent changes in the expression of endothelial nitric oxide-synthase, leading to increased nitric oxide production, vasodilation of blood vessels, and upregulation of antioxidant genes (e.g., Nrf2), and reduction of proinflammatory cytokines in vascular cells [25; 52].

Diabetes: ASSOCIATED WITH LOWER RISK AND BETTER METABOLIC INDICES
In a 2016 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 [53]. 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) [32]. 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 [54]. 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 a 2021 meta-analysis of 12 randomized controlled trials including a total of 662 people with type 2 diabetes, soy protein and soy isoflavone treatment significantly decreased total cholesterol (–0.21 mmol/L; 95% CI, –0.33 to –0.09; p=0.0008) and LDL-cholesterol (–0.20 mmol/L; 95% CI, –0.28 to –0.12; p<0.0001) compared to the control [55]. There were no significant changes in HDL-cholesterol, triacylglycerols, fasting glucose, insulin, HbA1c, or HOMA-IR (changes in glucose metabolism) after soy isoflavone treatment. However, in a subgroup analysis, people at or under the age of 60 showed significantly lower HbA1c levels with soy isoflavone supplementation (p<0.0001).

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) [56].

Obesity/Metabolism: UNCLEAR
In a 2018 meta-analysis of 23 randomized controlled trials including a total of 1,889 postmenopausal women, phytoestrogen supplementation (soy isoflavones, red clover isoflavones, flaxseed extract, etc.) did not significantly affect body weight, body mass index, waist and hip circumference, total fat mass, or percentage of body fat [57]. However, phytoestrogen treatment was associated with a slight decrease in waist-to-hip ratio; the pooled mean difference was -0.01 cm (95% CI, -0.01 to -0.006). In a subgroup analysis, a modest decrease in body weight with phytoestrogens supplementation was found compared with placebo in healthy postmenopausal women (pooled mean difference=-0.28 kg; 95% CI, -0.52 to -0.04). In contrast, phytoestrogen treatment was associated with an increase in body weight in postmenopausal women with preexisting metabolic disorders (prediabetes, type 2 diabetes, prehypertension and hyperlipidemia) (pooled mean difference=0.78 kg; 95% CI, 0.53 to 1.03).

In a small randomized controlled trial of 23 healthy older men and women, unsalted soy nuts (67 g/day) that provided 174 mg isoflavones per day for 16 weeks did not significantly alter body weight, body mass index, body fat percentage, fasting glucose, fasting insulin, or the HOMA-IR (insulin resistance index) [16]. However, the soy nut intervention reduced waist-to-hip ratio by 0.02 at follow-up (p=0.045).

Osteoporosis: BENEFIT
Peak bone mass is reached by the end of the second decade of life, but around the age of 40, there is a gradual decrease in bone mass, and at the fifth decade of age, there is an accelerated bone loss [58]. The rate of bone loss increases a few years before menopause in women, and during the menopause transition period, the average reduction in bone mineral density is about 10% [59]. The decline in estrogen levels during menopause is the main cause of accelerated bone turnover. Hormone replacement therapy has been shown to prevent bone loss and reduce fractures in postmenopausal women who do not already have osteoporosis, but risks of hormone therapy have to be weighed against the benefits [60]. Because total bone remodeling cycle takes about 160 days, studies with short intervention durations may be insufficient to assess the effects on bone mineral density.

A 2016 systematic review of 23 double-blind randomized controlled trials has reported potentially protective benefits of soy isoflavone supplementation, though the data were mixed [61]. 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].

In a 2022 meta-analysis of numerous randomized controlled trials in postmenopausal women, daily intake of 106 mg (range, 40-300 mg) for 6-24 months moderately but statistically significantly increased bone mineral density in the lumbar spine (weighted mean difference [WMD]=1.63, 95% CI, 0.51 to 2.75; p=0.004), femoral neck (WMD=1.87; 95% CI, 0.14 to 3.60; p=0.034), and total hip (WMD=0.39; 95% CI, 0.08 to 0.69; p=0.013)[62]. The soy phytoestrogen treatments varied across studies and included a single isoflavone (e.g., genistein), soy isoflavone extracts, soy protein isolate, and other isoflavone preparations. Subgroup analyses showed a statistically significant effect of isoflavone consumption on lumbar spine bone mineral density in Caucasian women. For reference, Asian women consume on average 25-45 mg of isoflavones per day compared to 5 mg per day by Western women.

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.

Inflammation: MIXED
In a 2023 meta-analysis of 10 randomized controlled trials including a total of 1,052 people with chronic inflammatory disorders, soy isoflavone treatment (33-132 mg/day) for 4-96 weeks did not significantly reduce serum concentration of C-reactive protein (CRP) [63]. However, subgroup analyses showed that soy isoflavone treatment significantly reduced CRP levels in studies among participants with age over 57 years and baseline CRP levels over 3.75 mg/L

In a 2023 meta-analysis of randomized controlled trials in older adults, treatment with isolated soy proteins significantly reduced TNF-α levels (mean difference [MD]=-0.16; 95% CI, -0.26 to -0.05) and the addition of soy isoflavones exerted further decline in TNF-α levels (MD=-0.20; 95% CI, -0.31 to -0.08)[64].

Oxidative stress: BENEFIT
In a 2020 meta-analysis of 24 randomized controlled trials including 1,852 participants with various conditions (menopause, diabetes, metabolic syndrome, NAFLD, PCOS, cardiomyopathy, dyslipidemia, etc.), soy intake significantly reduced levels of the oxidative stress marker, MDA (SMD=-0.53; 95% CI, -0.86 to -0.19), and significantly increased antioxidant defenses measured by GSH levels (SMD=0.53; 95% CI, 0.08 to 0.99), total antioxidant capacity (SMD=0.54; 95% CI, 0.27 to 0.82), and total reactive

antioxidant potential (SMD=1.74; 95% CI, 0.82 to 2.65) compared to the control group [65]. Ten randomized controlled trials used soy isoflavones as an intervention while other studies used soy proteins, soybeans, soy nuts, or soy milk. Subgroup analyses based on the type of soy intervention showed that soy isoflavones were more efficient in reducing MDA levels compared to soy protein products and soy milk.

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 [66]. 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 [67]. 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 [68].

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)[69]. 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 [70]. 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 a retrospective responder analysis of a phase 1b/2a study, participants treated with the 50 mg dose of PhytoSERM (16.7 mg/day each of genistein, daidzein, and S-equol, orally) showed significantly reduced hot flash frequency compared with their baseline (mean=-1.61; p=0.007) and compared with the placebo group (PhytoSERM group, -1.38; placebo group, -0.17; p=0.04) [5]. This effect of PhytoSERM was not seen with the 100 mg dose. When stratified by mitochondrial haplogroup, people in the mitochondrial haplogroup H had significantly decreased hot flash frequency when treated with 50 mg of PhytoSERM per day compared with placebo (−1.64 vs 0.43; p=0.04). Women who were in a non-H haplogroup had comparable reduction in hot flash frequency compared with the haplogroup H participants, but due to the high variation within the group, the difference was not statistically

significant (p=0.15). When stratified by APOE genotype, APOE4 noncarriers receiving 50 mg/day PhytoSERM had significantly greater reduction in hot flash frequency compared with those receiving placebo (−0.86 vs 0.21; p=0.04). A trend towards reduced hot flash frequency was observed in APOE4 carriers, but due to the limited sample size, the difference was not statistically significant (−2.29 vs −0.57; p=0.17).

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. Soy isoflavone treatment does not alter levels of hormones such as testosterone and estradiol.

Types of evidence:

- 5 meta-analyses based on randomized controlled trials
- 1 systematic review based on 131 studies (40 RCTs, 11 uncontrolled, 80 observational)
- 6 randomized controlled trials

A 2015 meta-analysis of 10 randomized controlled trials including 1,024 menopausal women reported that no statistically significant differences in adverse events were seen between soy isoflavone supplementation and placebo [7]. 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 [69]. There was one trial where the placebo group experienced significantly more side effects than those in the soy/phytoestrogen group.

A 2020 meta-analysis of 16 randomized controlled trials including a total of 1,386 participants (1,252 of whom were postmenopausal women) reported that treatment with soy isoflavones (60 to 160 mg/day, orally) for 6-130 weeks did not lead to serious adverse events, and other adverse events were similar to those in placebo groups [8].

Individual randomized controlled trials, including one in Alzheimer's patients, reported good safety profiles with soy isoflavone interventions [9; 12; 15; 19]. Adverse events were generally mild [9] and no abnormal lab values were observed [19].

In a phase 1b/2a double-blind randomized controlled trial of 71 cognitively unimpaired peri-menopausal women (age 45-60), treatment with soy isoflavones (PhytoSERM; 50 and 100 mg/day, orally; 16.7 or 33.3 mg each of genistein, daidzein, and S-equol) for up to 12 weeks was well-tolerated, with mostly mild (85%) adverse events occurring in 39.1% (n=9) people in the 50 mg daily PhytoSERM group, 29.2% (n=7) in the 100 mg daily PhytoSERM group, and 16.7% (n=4) in the placebo group [13]. No adverse events were severe. Incidences and types of adverse events were not related to dose. Vaginal bleeding occurred in 1 woman receiving the 50 mg daily dose, 3 women receiving the 100 mg daily dose, and none in the placebo group. The authors noted the possibility of ERα activation as a possible cause of vaginal bleeding. The possible peripheral ERα activation with PhytoSERM will require further surveillance. Nausea and headaches occurred more frequently with PhytoSERM treatment compared to placebo. One participant in the 50 mg daily PhytoSERM group discontinued within the first 4 weeks; 3 discontinued during weeks 5 to 8 (1 in 50 mg PhytoSERM, 2 in 100 mg PhytoSERM), and 1 discontinued during weeks 9 to 12 (50 mg PhytoSERM group). Overall, 93% of participants who were randomized completed the 12-week trial. Reasons for dropout were lost to follow-up (4 participants) and withdrawal of consent out of concern about becoming dependent on the treatment and not being able to obtain it after the trial (1 participant). No participant withdrew due to an adverse event.

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 [40].

In a meta-analysis of 41 clinical trials and single-group studies including a total of 1,753 healthy men or men with prostate cancer, treatment with soy foods, soy protein, or isoflavones (0-600 mg/day) did not significantly alter levels of total testosterone, free testosterone, estradiol, or estrone [71]. Subgroup analyses showed that neither study duration (≤12 weeks vs >12 weeks) nor isoflavone dose (<75 mg daily vs ≥75 mg daily) affected the impact on these hormone levels.

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 [10; 15; 18]. However, soy isoflavone doses of 100 mg/day for 6 months did not improve cognitive function in Alzheimer's patients [19].

Research underway:

A double-blinded, randomized, placebo-controlled proof-of-concept phase 2 clinical trial is investigating the safety and efficacy of the phytoestrogenic supplement, PhytoSERM, in preventing menopause-associated decline in brain metabolism (measured by FDG-PET) in peri- and post-menopausal women (NCT05664477). This trial is enrolling 100 participants who will be assigned to PhytoSERM treatment (50 mg once daily, orally) or matching placebo for 24 weeks. The study is estimated to be completed in February 2028.

There are several other ongoing clinical trials testing soy isoflavones (ClinicalTrials.gov): 1 in breast cancer, 1 in skin aging, 1 in asthma in infants, and several child development studies.

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
- Drugs.com
- WebMD.com
- Labdoor.com (0)
- Patientslikeme

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