Phytoestrogens (Isoflavones and Lignans)

Sources and Physiological Functions

Phytoestrogens are naturally occurring polyphenolic compounds found in many plant-based foods. Because their structure is similar to 17β-estradiol, they can bind to estrogen receptors and influence estrogen signaling. The two main classes relevant to human health are isoflavones, which are abundant in soy products, and lignans, which are present in seeds, whole grains, and vegetables (Pejčić 2023; Senizza 2020). Interest in phytoestrogens and cancer risk stems from epidemiologic observations of lower breast and prostate cancer incidence in populations with high soy intake. At the same time, their combined estrogenic and anti-estrogenic actions have raised questions about their effects on hormone-dependent cancers. This report considers urine concentrations of two dietary isoflavones (daidzein, genistein), two daidzein metabolites (O-desmethylangolensin [ODMA] and equol), and two lignan metabolites (enterodiol and enterolactone).

Isoflavones occur at their highest concentrations in soybeans, soy-derived products (soy flour, soy milk, soy protein isolate) and traditional soy-based foods (tofu, miso, tempeh) (Reinli 1996; Manach 2004). Processed meats, meat substitutes, breads, and protein-food bars can also be dietary sources of isoflavones because of the use of soy flour or soy protein isolates in their production (Lampe 1999; Grace 2004). Isoflavone concentrations in soy-based products vary widely depending upon production techniques (Erdman 2004). The major isoflavones found in soy are daidzein and genistein, which occur in soy as sugar conjugates (glycosides). Non-soy dietary sources of daidzein and genistein also exist. Kudzu root, an ingredient used in dietary supplements, is known to contain appreciable amounts of daidzein and genistein (Kaufman 1997). Red clover, also used in dietary supplements, contains significant amounts of formononetin and biochanin A, compounds which can be metabolized by the human intestine to daidzein and genistein, respectively (Reinli 1996; Manach 2004). Lignans are found in flax seeds, whole wheat flour, tea, some fruits, and other cereal grains. Lignans include matairesinol and secoisolariciresinol, which are transformed by intestinal bacteria into the estrogenic compounds enterolactone and enterodiol, respectively (Rowland 2003; Cornwell 2004). Enterodiol may also change into enterolactone and vice versa. Isoflavone intake is typically higher in Asian populations than in Western populations (Messina 2024). The higher intake is primarily due to the higher soy consumption and the significant role that such fermented food products (like tempeh, miso, or

natto) play in Asian diets (Mortensen 2009). Lignan intake varies greatly from country to country because of different dietary sources; however, completeness of food composition data is also a confounding factor in interpreting these data (Peterson 2010).

How individuals absorb and metabolize phytoestrogens varies. The variation may relate to differences in how intestinal bacteria process absorption, enterohepatic circulation, and metabolism. Isoflavones and lignans occur primarily as glycosides in unfermented foods with a small percentage of aglycones present. Aglycones represent a larger portion of the phytoestrogens present in fermented foods due to bacterial hydrolysis of the glycosides. Glycosidic forms are hydrolyzed to their aglycones in the intestine, absorbed, and then linked in the intestinal wall and liver with glucuronic acid to make them more water-soluble. This process is known as glucuronidation. The glucuronidated metabolites of isoflavones predominate in blood and urine (Doerge 2000; Rowland 2003; Clavel 2006; Nielsen 2007). Ingested daidzein is further metabolized to ODMA and to equol by intestinal bacteria. Equol, but not ODMA, has estrogenic activity. About 30% of adults produce equol and have higher serum equol concentrations after they consume daidzein (Setchell 2003; Cassidy 2006a). The ability to produce equol may be related to an individual's intestinal microflora and influenced by dietary habits and genetic factors (Rowland 2000; Setchell 2002; Setchell 2006). It is unclear whether the ability to produce equol results in any health-related effects (Vafeiadou 2006).

Generally, phytoestrogens are much less potent than endogenously produced estrogens, but phytoestrogens can be present in much greater quantities (100 to 1000 times the concentration of endogenous estrogens). Additionally, phytoestrogens bind less tightly to steroid-hormone serum-transport proteins than do endogenous estrogens (Nagel 1998). Equol has more potent estrogen activity than its precursor daidzein. In addition, equol has been proposed to be most important in explaining the possible mechanism of action of isoflavones in disease prevention (Setchell 2002).

Health Effects

The potential role of phytoestrogens, such as isoflavones and lignans, in modulating hormone-dependent cancer risk has been extensively investigated, particularly for breast, prostate, and endometrial cancers. Beyond their role in hormone-dependent cancers, these compounds have also been studied for effects on cardiovascular health, bone metabolism, menopausal symptoms, metabolic disorders, and neurocognitive function (Canivenc-Lavier 2023; Rietjens 2017).

Isoflavones and lignans act as weak ligands for estrogen receptors, with a preference for binding to estrogen receptor (ER)-β. Activation of ER-β is linked to anti-proliferative effects in breast and prostate tissues (Pejčić 2023). Because these compounds bind less strongly than estradiol, they can behave as partial agonists or antagonists, depending on circulating hormone levels. Phytoestrogens also influence key enzymes involved in steroid hormone synthesis, such as aromatase and 17β-hydroxysteroid dehydrogenases. Through these actions, they may lower circulating estrogen levels or shift estrogen metabolism toward less biologically active metabolites (Chakravarti 2024). Isoflavones and lignans may also modulate antioxidant processes and inflammatory pathways, reducing oxidative stress and contributing to protection against cardiovascular and neurodegenerative diseases (Gorzkiewicz 2021), as well as influence lipid metabolism, glucose homeostasis, and insulin signaling, providing a mechanistic basis for potential effects on metabolic syndrome and type 2 diabetes (Cornwell 2004).

Meta-analyses of observational studies suggest that higher isoflavone intake is associated with a lower risk of breast cancer, with evidence of a dose-response relationship (Yang 2023). The protective association appears stronger in Asian populations, possibly reflecting higher lifelong exposure to soy and other isoflavone-rich foods. Overall, current evidence does not indicate that soy intake increases breast cancer risk. Instead, moderate consumption appears neutral or protective, particularly among postmenopausal women (Chakravarti 2024). Studies of women with a previous breast cancer diagnosis similarly suggest that isoflavone intake does not increase recurrence risk and may improve survival. A recent meta-analysis found no adverse association between phytoestrogen intake and breast cancer prognosis (van Die 2024). Meta-analyses also indicate that lignan intake is associated with a reduced risk of breast cancer in postmenopausal women, although the effect sizes are modest and the findings heterogeneous (Buck 2010). Higher lignan intake and higher circulating enterolactone levels have been linked to improved survival, particularly in postmenopausal women, but evidence for such associations in premenopausal women is less consistent (Liu 2021).

Isoflavones have also been linked to a modest reduction in prostate cancer risk. In a pooled analysis of prospective studies, higher circulating isoflavone levels were inversely associated with prostate cancer risk in Japanese men but not in European cohorts, underscoring the importance of exposure levels and dietary patterns (Perez-Cornago 2018). In contrast, current evidence does not

support a clear association between lignan exposure and prostate cancer risk, and biomarker-based studies generally report null findings (Perez-Cornago 2018).

Evidence regarding isoflavones and endometrial cancer is limited but suggests a possible inverse association. Some case-control studies report a reduced risk with higher isoflavone intake, although results are not consistent across all populations (Horn-Ross 2003; Bandera 2009). Similarly, some observational studies suggest that higher lignan intake may be associated with a lower risk of endometrial cancer, but the overall evidence remains limited and inconsistent (Bandera 2009).

Isoflavones have been linked to modest reductions in LDL cholesterol and inhibition of LDL oxidation, both relevant to atherosclerosis (Lissin 2000; Cassidy 2006b). Some systematic reviews report LDL decreases of about 0.15 mmol/L with soy protein containing isoflavones, though effects on HDL and triglycerides are inconsistent. Phytoestrogens appear to improve endothelial function and vascular reactivity, likely via estrogen receptor–mediated nitric oxide pathways and antioxidant effects (Gencel 2012), and epidemiologic data associate higher phytoestrogen intake with lower cardiovascular disease prevalence in soy-consuming populations (Rietjens 2017). Enterolignans have been associated with improved lipid profiles and lower triglycerides in some studies, although results are modest and inconsistent (Canivenc-Lavier 2023).

Randomized controlled trials suggest that soy isoflavone supplementation may modestly increase lumbar spine bone mineral density, with less consistent effects at other skeletal sites, likely through estrogen receptor–mediated promotion of osteoblast activity and reduced bone resorption (Canivenc-Lavier 2023). Observational studies also report lower fracture rates with higher phytoestrogen intake (Tham 1998).

Soy isoflavones have been investigated as alternatives to hormone replacement therapy, and some meta-analyses show reductions in hot flashes and other vasomotor symptoms, although findings are heterogeneous and influenced by placebo effects and individual variability; nonetheless, phytoestrogens are widely used as non-hormonal options for menopausal symptom management and generally have favorable safety profiles (Canivenc-Lavier 2023).

Phytoestrogens may also influence insulin sensitivity and glucose metabolism, with observational and mechanistic studies suggesting possible benefits for type 2 diabetes and metabolic syndrome, although evidence is inconsistent and often modest; some data indicate potential effects on

adiposity via modulation of lipid metabolism and energy balance, but results remain inconclusive (Canivenc-Lavier 2023).

In addition, phytoestrogens have been proposed to exert neuroprotective effects, potentially lowering the risk of cognitive decline and neurodegenerative diseases through antioxidant and anti-inflammatory actions in neural tissue, modulation of neuronal signaling, and estrogen receptor–mediated neuroprotection, which may contribute to reduced risk of conditions such as Alzheimer's disease (Gorzkiewicz 2021).

Current evidence supports low concern about toxicity from usual adult isoflavone intake, but does not eliminate uncertainty for children, pregnancy, or individuals with thyroid vulnerability. In 2006, a National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) expert panel on purified genistein found no human data on reproductive or developmental toxicity, but judged animal evidence sufficient to show such toxicity in rodents. Even so, it expressed negligible concern for adults at then-current exposure levels and for infants exposed to genistein aglycone via soy formula, with one dissenting panelist for infants (Rozman 2006a). NTP-CERHR's 2006 soy formula review considered human and animal data insufficient to determine developmental or reproductive toxicity, while the updated 2010 NTP-CERHR monograph concluded there was minimal concern for adverse developmental effects in infants consuming soy formula (Rozman 2006b; McCarver 2011). Subsequent adult data are broadly consistent. A 2015 review by the European Food Safety Authority (EFSA) found no evidence of harmful effects on the mammary gland, uterus, or thyroid at isoflavone doses typical of menopausal supplements (EFSA 2015), and a 2015 meta-analysis of 40 randomized trials found no significant effects of soy isoflavones on endometrial thickness, vaginal maturation index, follicle-stimulating hormone, or estradiol in postmenopausal women (Viscardi 2025). Thyroid and male reproductive data are similarly reassuring for most adults. A 2019 meta-analysis reported no significant change in free triiodothyronine-3 or free thyroxine-4 and only a very small rise in thyroid-stimulating hormone of uncertain clinical relevance (Otun 2019). A 2021 meta-analysis found no adverse effect on male reproductive hormones (Reed 2021). Uncertainty remains for susceptible groups and for chronic high exposure. Among people with subclinical hypothyroidism, one 8-week crossover trial found higher progression to overt hypothyroidism with 16 mg/day soy phytoestrogens (Sathyapalan 2011), whereas a later crossover study using 66 mg/day did not detect increased thyroid failure or altered thyroid tests (Sathyapalan 2018).

Current human data do not convincingly link usual dietary lignan intake to endocrine, thyroid, or reproductive toxicity, but lack long-term, high-dose studies. A 12-week randomized trial with 25 g/day flaxseed (about 46 mg lignans/day) did not affect endometrial thickness or thyroid or hormonal measures in postmenopausal women (Simbalista 2010). A 12-month placebo-controlled trial with 50 mg/day of a flaxseed lignan (secoisolariciresinol diglucoside) produced similar adverse-event rates to placebo with no evidence of harm (Fabian 2020).

Biochemical Indicators

A systematic review of intervention studies showed that urine concentrations of daidzein, genistein, and enterolactone are good biomarkers of dietary intake (Pearson *r*: 0.78–0.87) as compared to equol, ODMA (0.38–0.40), and enterodiol (-0.14) (Pérez-Jiménez 2010). Linear dose-response relations are typically observed for the lignans (Nesbitt 1999; Hutchins 2000). Saturation in urine recovery has been observed with the isoflavones (Setchell 2003).

Analytical Methods

Isoflavones and lignans have been measured in biologic matrices such as plasma, serum, and urine using high-performance liquid chromatography (HPLC) or gas chromatography (GC) with various modes of detection (Hoikkala 2003; Prasain 2004). HPLC-mass spectrometry (HPLC-MS/MS) methods that measure isoflavones and lignans concentrations after deconjugation of glucuronides and sulfates esters (Rybak 2008; Parker 2011) are commonly used in population studies where researchers want to assess total exposure.

Findings from NHANES

The National Health and Nutrition Examination Survey (NHANES) is the only source for nationally representative data on urine phytoestrogen biomarkers for the U.S. population (Pfeiffer 2026). These compounds have been measured in NHANES from 1999–2010. In NHANES 1999–2000, CDC scientists detected enterolactone in the highest concentration, and daidzein was detected with the highest frequency among the six measured phytoestrogens (Valentin-Blasini 2005). CDC's Fourth National Report on Human Exposure to Environmental Chemicals presented geometric means and selected percentiles (50th, 75th, 90th, and 95th) for concentrations of phytoestrogens by age, sex, or race/ethnicity for participants in NHANES 1999–2000, 2001–2002, and 2003–2004 (U.S. Centers for Disease Control and Prevention 2009). CDC's Second National Report on Biochemical Indicators of Diet and Nutrition in the U.S. Population presented geometric means and selected percentiles (50th, 75th, 90th, and 95th) for concentrations of phytoestrogens by age, sex, or race/ethnicity for participants in NHANES 1999–2000, 2001–2002, and 2003–2004 (U.S. Centers for Disease Control and Prevention 2012).

A multiple regression analysis of NHANES 2003–2006 showed that together, sociodemographic (age, education, income, race-ethnicity, and sex) and lifestyle (alcohol consumption, body mass index, dietary supplement use, physical activity, and smoking) variables explained between 1% and 4% of the urine phytoestrogen biomarker variability and between 8% and 17% after additionally

controlling for urine creatinine (Rybak 2013). Another multiple regression analysis of NHANES 2003–2006 showed that after controlling for demographic variables, smoking, supplement use, fasting, inflammation, and renal function, inflammation was associated with significantly lower concentrations for the lignans enterolactone (-37.9%) and enterodiol (-20.8%) and for the daidzein metabolite ODMA (-35.5%). Fasting and renal function were not associated with any of the six phytoestrogens (Haynes 2013).

For more information about soy isoflavones, see the fact sheet from the National Institutes of Health, Office of Dietary Supplements (https://ods.od.nih.gov/factsheets/list-all/).

Data in the 2026 tables

Data presented are from univariate analysis that was not adjusted for demographic variables (e.g., age, sex, race and Hispanic origin) or other blood concentration determinants (e.g., dietary intake, supplement use, smoking, BMI). Data for the urine phytoestrogens were available from different NHANES cycles (1999–2010) and have been generated using HPLC-MS/MS methods with different ionization techniques: atmospheric pressure chemical ionization (APCI) for 1999–2000 (Valentin-Blasini 2000), APCI for 2001–2002 (Kuklenyik 2004), electrospray ionization (ESI) for 2003–2004 (Rybak 2008), atmospheric pressure photoionization (APPI) for 2005–2006 (Parker 2011), and ESI for 2007–2010. Crossover studies comparing samples analyzed by HPLC-ESI-MS/MS and HPLC-APPI-MS/MS demonstrated high correlation coefficients ($r > 0.99$) and regression slopes approximately equal to 1 and intercepts close to 0 (U.S. Centers for Disease Control and Prevention 2011). Thus, no data adjustments were needed to allow for comparisons over time. Phytoestrogen data are shown for both the urine concentration and for the concentration corrected for the urine creatinine level.

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