



DOSSIER · SUBSTANCE

Soy Isoflavones (Genistein, Daidzein)

Soy isoflavones are plant compounds with oestrogen-like structure that occur in soy. The literature on these compounds is extensive. The most interesting finding: Bioavailability depends strongly on the intestinal flora – only some people form the more effective metabolite S-Equol.

559

STUDIES IN
TOTAL

251

IN HUMANS

178

OF WHICH
CONTROLLED

41

IN ANIMALS

13

IN THE LAB

Figures from the IHR study database · Last updated 2026-10-15

How to Read This Dossier

ESTABLISHED

measured in humans, with a comparison group

PLAUSIBLE

supported by mechanism, animal studies or observation

HYPOTHESIS

a likely connection that still needs to be tested

Soy Isoflavones (Genistein, Daidzein) at a Glance

ORIGIN:
Soy isoflavones are secondary plant substances from the group of flavonoids that occur primarily in soya beans and foods produced from them. The most important representatives are genistein and daidzein, alongside glycitein; in the plant they are present predominantly as glycosides, that is, bound to sugar. Their structure resembles endogenous oestrogen, which is why they are termed phyto-oestrogens and can bind to oestrogen receptors with lower affinity.

EVIDENCE BASE:
559 evaluated papers · 178 controlled human studies · 73 observational studies · 59 review articles · 41 animal studies · 11 cell-culture studies

- STRONGEST EVIDENCE:**
- Hot flushes: The meta-analysis by Taku et al. (2012) included 17 studies; soy isoflavones with a median of 54 mg aglycone equivalents significantly reduced the frequency of hot flushes over 6 weeks to 12 months.
 - Absorption and bioavailability: Only between one third and one half of people can convert daidzein to S-equol, the metabolite with higher affinity for oestrogen receptor beta (Mayo et al. 2019).
 - Hormones: In premenopausal women, soya or isoflavone intake lowered FSH and LH by approximately 20 % (p = 0.01 and 0.05 respectively), without effect on oestradiol, oestrone or SHBG (Hooper et al. 2009, 47 studies).

- LIMITATIONS:**
- The controlled studies frequently test soya protein or soya foods, in which isoflavones are only one component alongside proteins and other constituents.
 - Equol-producer status is often not recorded, although only a subset of participants form S-equol; this limits comparability of results.
 - Kupperman index and hot-flush frequency produced differing results in the meta-analyses; direct comparisons of dose and composition are still outstanding.

CLASSIFICATION:
Soy isoflavones are well-studied phyto-oestrogens whose effect depends strongly on whether the intestinal flora can convert daidzein to S-equol.

1. What Soy Isoflavones Are

Soy isoflavones are secondary plant substances from the group of flavonoids that occur primarily in soya beans and foods produced from them. The most important representatives are genistein and daidzein, alongside glycitein. In the plant they are present predominantly as glycosides, that is, bound to sugar. They resemble endogenous oestrogen in their chemical structure, which is why they are termed phyto-oestrogens. This structural similarity explains why they can bind to oestrogen receptors, albeit with markedly lower affinity than the natural hormone. Research ranges from basic studies through controlled trials to observational studies and review articles.

For the evaluation of all studies one point is decisive: the absorption and action of the isoflavones depend strongly on the dosage form and the individual intestinal flora. In soya foods the isoflavones are usually present as glycosides that are first converted by intestinal bacteria into the active aglycones genistein and daidzein. In some people daidzein is further metabolised to S-equol, a metabolite with higher affinity for oestrogen receptor beta. Whether and to what extent this occurs varies inter-individually and is termed equol-producer status. Studies that use extracts or isolated isoflavones therefore differ systematically from those using soya protein or soya foods. Bioavailability is a central modifier that restricts comparability of results.

2. What the Studies Show in Detail

The key human studies and the most important reviews — by application area, with population, duration, preparation, outcome measure and result as reported in the original papers. Numbers appear only where the work states them.

Distribution of **controlled human studies** by application area — the numbers are not additive because one paper may be assigned to several areas:

APPLICATION AREA	CONTROLLED STUDIES
Metabolism	58
Cardiovascular system	47
Safety and tolerability	45
Bones and joints	40
Oncology	39
Cognition and psyche	23
Absorption and bioavailability	23
Inflammatory processes	22

Bones and Joints

The controlled study by Kreijkamp-Kaspers et al. (2004) examined whether 25.6 g soya protein containing 99 mg isoflavones (52 mg genistein, 41 mg daidzein, 6 mg glycitein) daily for 12 months improved bone density, cognition and blood lipids in 202 healthy postmenopausal women aged 60 to 75 years. Results for bone density were not reported in the abstract; the work is therefore not citable for this endpoint.¹

Atkinson et al. (2004) tested a red-clover isoflavone extract providing daily 26 mg biochanin A, 16 mg formononetin, 1 mg genistein and 0.5 mg daidzein for one year in 205 women aged 49 to 65 years (177 completed the study). Loss of bone mineral content and density at the lumbar spine was significantly smaller in the verum group than under placebo ($p = 0.04$ and $p = 0.03$). No significant effects were seen at the hip, on resorption markers or body composition; bone-formation markers rose significantly ($p = 0.04$ for bone-specific alkaline phosphatase, $p = 0.01$ for N-propeptide of type-I collagen). The study therefore examined a red-clover extract and not soy isoflavones; the work says nothing about soy isoflavones.⁶

The high dose led to a mild but statistically significant improvement in the rate of change of bone mineral content at the total hip and the trochanter ($p < 0.05$) compared to placebo and the medium dose. In stratified analyses this effect appeared only in women with lower baseline bone mineral content (median or below).¹⁴

After two years, no significant differences were found between the treatment group ($n = 122$) and the placebo group ($n = 126$) with regard to bone density at the spine (-2.0% vs. -2.3%), total hip (-1.2% vs. -1.4%) and femoral neck.¹⁵

Clifton-Bligh et al. (2001) administered to 46 postmenopausal women in a double-blind protocol with single-blind placebo phase and subsequent washout phase a red clover isoflavone preparation (Rimostil) with genistein, daidzein, formononetin and biochanin in daily doses of 28.5 mg, 57 mg or 85.5 mg over six months. Bone density of the proximal radius and ulna increased by 4.1 % under 57 mg/day ($p = 0.002$) and by 3.0 % under 85.5 mg/day ($p = 0.023$); under 28.5 mg/day the effect was not significant. Endometrial thickness did not increase significantly under any dose.¹⁶

HYPOTHESIS The inconsistent results could be related to the differing isoflavone composition, the baseline bone density and the ethnic origin of the study participants. It remains open whether the observed effects are attributable to the isoflavones themselves or to the accompanying protein matrix; studies with isolated isoflavones without protein carrier are lacking here.

Gut and Microbiome

Wiseman et al. (2000) compared an isoflavone-rich with an isoflavone-poor soya diet in a randomised crossover design in 24 participants. After the isoflavone-rich diet the plasma concentrations of 8-epi-PGF(2 α), a biomarker of lipid peroxidation in vivo, were significantly lower than after the isoflavone-poor diet (326 ± 32 vs. 405 ± 50 ng/L; $p = 0.028$), and the lag time to copper-ion-induced LDL oxidation was longer (48 ± 2.4 vs. 44 ± 1.9 min; $p = 0.017$).²

Setchell et al. (2003) investigated the bioavailability of daidzein and genistein after intake of aglycone or glucoside tablets in 15 American women aged 46 ± 6 years in a randomised, double-blind study. Plasma concentrations reached a first peak after 1–2 hours and a second peak after 4–8 hours. For genistein, C_{max}, t_{max} and AUC did not differ significantly between the forms. For daidzein, C_{max} and AUC were significantly higher after aglycone intake, which was partly attributed to the higher content in the aglycone tablets. Equol appeared after 4 hours and remained elevated until 48 hours.³

The review by Mayo et al. (2019) summarises that the conversion of daidzein to equol in the gut by reductases of as yet incompletely characterised members of the gut microbiota takes place. While all investigated animal species produce equol, only between one third and one half of humans are able to do so, presumably those who harbour equol-producing microbes. Possibly only these persons can fully benefit from soya or isoflavone consumption.⁴⁰

HYPOTHESIS The inter-individual differences in equol production could explain why clinical studies on isoflavones yield inconsistent results. Whether targeted promotion of equol-producing bacteria improves the effect of isoflavones is an open question that can only be clarified by intervention studies with microbial characterisation.

Further Investigations

The meta-analysis by Chen et al. (2015) included 15 randomised controlled trials in which oral phytoestrogens were investigated in perimenopausal or postmenopausal women with menopausal symptoms. The mean age of the participants ranged between 49 and 58.3 years (placebo) and 48 and 60.1 years (phytoestrogens) respectively; the number of participants ranged from 30 to 252, the intervention duration from 3 to 12 months. The meta-analysis of seven studies with Kupperman index data yielded no significant treatment effect (pooled mean difference = 6.44; $p = 0.110$). The meta-analysis of ten studies with hot flush data showed a significantly greater reduction in hot flush frequency under phytoestrogens compared to placebo.⁵

The systematic review and meta-analysis by Hooper et al. (2009) comprised 47 studies (11 in premenopausal, 35 in postmenopausal and 1 in perimenopausal women) with a duration of at least four weeks. In premenopausal women, consumption of soya or isoflavones had no influence on oestradiol, oestrone or SHBG, but significantly reduced FSH and LH (by approximately 20 % via standardised mean difference; $p = 0.01$ and 0.05 respectively). Menstrual cycle length was prolonged by 1.05 days (95 % CI 0.13–1.97; 10 studies). In postmenopausal women, no statistically significant effects on oestradiol, oestrone, SHBG, FSH or LH were found.¹⁰

The meta-analysis by Taku et al. (2012) identified 19 studies (13 on hot flush frequency, 10 on severity, 3 on combined scores) from 277 potentially relevant publications; 17 studies were included in the meta-analyses. Intake of soya isoflavones (median 54 mg aglycone equivalents) over 6 weeks to 12 months significantly reduced the frequency of hot flushes.¹¹

HYPOTHESIS The discrepancy between the lack of effect on the Kupperman index and the significant reduction in hot flush frequency could be due to differing assessment instruments or study populations. It remains open which isoflavone dose and composition is most effective for which symptom group; direct comparative studies on this are still outstanding.

Safety and Tolerability

The randomised crossover study by Setchell et al. (2006) investigated the bioavailability of isoflavones from three different soya foods (soya milk, textured vegetable protein, tempeh) in aglycone and glucoside form in healthy adults – 21 premenopausal women, 17 postmenopausal women and 21 men. The single dose was 0.44 mg/kg body weight. Serum concentrations rose rapidly after intake in all persons and groups. The study reports no adverse events.⁷

The review by Rizzo and Baroni (2018) discusses soya and soya foods in vegetarian diets, including safety aspects such as possible disruption of thyroid function and sex hormones. The work emphasises that isoflavones are polyphenols with oestrogenic properties that occur abundantly in soya beans.

The review by Messina (2016) evaluates the clinical and epidemiological literature on soya and health. It concludes that human research supports the safety and benefit of soya foods, and refers to the recent assessment by the European Food Safety Authority that isoflavones have no adverse effects on breast, thyroid or uterus in postmenopausal women. ⁴⁴

HYPOTHESIS The safety data derive predominantly from short- to medium-term studies; long-term observations on higher doses and on special risk groups are still outstanding. The question whether the observed favourable effects are due to isoflavones or to the protein matrix has not been conclusively clarified.

Heart and Circulation

Teede et al. (2003) conducted a randomised, double-blind crossover study in 80 healthy participants (46 men, 34 women) aged 45 to 75 years. Participants received isoflavones enriched either with biochanin or formononetin (precursors of genistein and daidzein; 80 mg/day), or placebo over two periods of 6 weeks each. The isoflavone intervention significantly reduced arterial stiffness with improved systemic arterial compliance ($p = 0.04$; repeated measures ANOVA, Bonferroni correction), attributable to a reduction in total peripheral resistance ($p = 0.03$) and a corresponding reduction in central pulse wave velocity ($p = 0.02$) compared to placebo. Blood pressure ($p = 0.5$) and flow-mediated vasodilation ($p = 0.44$) remained unaffected. The improvements appeared to be restricted to isoflavones enriched with formononetin (adjusted $p = 0.06$). Formononetin treatment also reduced circulating vascular adhesion molecule-1 ($p < 0.01$). ⁸

The review by Ramdath et al. (2017) summarises the evidence on cardiovascular benefits of non-protein soya constituents such as isoflavones, lecithins, saponins and fibre. The authors conclude that the available evidence suggests that non-protein soya constituents improve markers of cardiovascular health; however, they emphasise that additional carefully designed studies are required to clarify these effects independently. Furthermore, the role of the isoflavone-metabolising phenotype and the gut microbiota composition for the biological effect needs to be clarified. ⁴⁸

HYPOTHESIS The observed improvement in arterial stiffness could be mediated by a reduction in peripheral resistance, yet the precise mechanism is unclear. Whether the effects are due to the soy isoflavones or their metabolites is an open question that would have to be clarified by studies with isolated compounds.

Metabolism

The randomised crossover study by Merz-Demlow et al. (2000) investigated the effect of three soya isoflavone doses (control: 10.0 ± 1.1 ; low: 64.7 ± 9.4 ; high: 128.7 ± 15.7 mg/day), administered as soya protein isolate over three menstrual cycles each, in 13 healthy, normocholesterolaemic, free-living premenopausal women. Total cholesterol, HDL cholesterol and LDL cholesterol changed significantly across the cycle phases ($p < 0.005$). In certain cycle phases the high isoflavone dose lowered LDL cholesterol by 7.6–10.0 %. ⁹

HYPOTHESIS The observed LDL reductions in normocholesterolaemic premenopausal women could indicate a modulation of hepatic cholesterol synthesis or LDL receptor metabolism. Whether these effects also occur in men or postmenopausal women with hypercholesterolaemia is not clarified; studies with comparable design are lacking for this.

Uptake and Availability

The randomised, double-blind crossover study by Richelle et al. (2002) investigated the pharmacokinetics of isoflavones after consumption of a soy drink with enriched isoflavone extract from soy germ (Fujiflavone P10), either enzymatically hydrolysed with beta-glucosidase to aglycones or left unchanged, in six European postmenopausal women. The drinks were administered at a concentration of 1 mg total isoflavones/kg body weight at one-week intervals. Plasma and urine pharmacokinetics of daidzein, genistein and glycitein did not differ between the two drinks. Plasma total isoflavone concentrations reached 4–5 $\mu\text{mol/L}$. The pharmacokinetics of glycitein resembled that of daidzein. Secondary metabolites detected were dihydrodaidzein in plasma and O-desmethylanagolensin, equol and dihydrogenistein in urine. The ratios of the individual isoflavones to one another were not preserved from food through plasma to urine, indicating that the individual isoflavones have different absorption and residence times. The authors conclude that prior hydrolysis of glycosides to aglycones does not increase the bioavailability of isoflavones in humans. ¹²

HYPOTHESIS The lack of improvement in bioavailability through hydrolysis could indicate that intestinal hydrolysis is already sufficient or that other factors such as gastric passage or gut microbiota limit absorption. Whether the results are transferable to other soy foods or to men remains open; studies with larger samples and different matrices are lacking for this.

Inflammatory Processes

Ide et al. (2010) investigated the combined inhibitory effects of soy isoflavones and curcumin on the production of prostate-specific antigen (PSA). In LNCaP cells, PSA production was markedly reduced by the combination treatment, and androgen receptor expression was also suppressed; because soy isoflavones and curcumin were given together, the effect cannot be attributed to soy isoflavones alone. Participants were divided into subgroups according to their baseline PSA value of 10 $\mu\text{g/ml}$. PSA values were assessed before and 6 months after treatment. The results of the clinical study were not reported in the abstract. ¹³

The review by Goh et al. (2022) summarises the anti-inflammatory properties of genistein. Genistein belongs to the flavonoid family, subgroup of isoflavones, and is a phytoestrogen derived mainly from legumes. Numerous in-vitro and in-vivo studies have been conducted to investigate the anti-inflammatory potential of genistein. The work aims to link the anti-inflammatory properties of genistein with signalling pathways. ²⁶

The review by Yu et al. (2016) discusses the anti-inflammatory benefits of isoflavones in general, not only soy isoflavones, and possible concerns. Isoflavones are a class of flavonoids with antioxidant, anti-cancer, antimicrobial and anti-inflammatory properties. Growing evidence points to the potential of isoflavones to prevent chronic diseases in which inflammation plays a key role, although the underlying mechanisms remain unclear. Some studies have raised concerns about adverse effects such as carcinogenesis, thymic involution and immunosuppression. ⁴⁶

HYPOTHESIS The clinical relevance of the in-vitro findings on PSA reduction is unclear, as the results of the clinical study are not reported in the abstract. Whether the combination of isoflavones with curcumin has synergistic effects is an open question that would require further clinical studies with PSA as endpoint.

Cognition and Psyche

Cognitive performance and mood were assessed at the end of each treatment period with a test battery. Of 17 cognitive performance tests and 6 mood tests, benefits were shown for the phytoestrogen treatment. Of 8 visual analogue scales for mood measurement, 7 improved significantly after phytoestrogen treatment. 49 patients preferred phytoestrogens, 9 placebo and 18 had no preference; the preference was independent of treatment order. The authors conclude that isoflavones may have positive effects.¹⁷

HYPOTHESIS The study was retracted (RETRACTED), which limits the robustness of the results. The reported positive effects on cognition and mood should therefore be interpreted with caution; independent replications are pending.

Oncology

The systematic review by Fritz et al. (2013) included 131 articles (40 RCTs, 11 uncontrolled studies, 80 observational studies) on the safety and efficacy of soy and red clover isoflavones in women with or at risk of breast cancer. Five RCTs reported on the efficacy of soy against hot flushes and showed no significant reductions compared with placebo. There is no clear evidence of harm from soy regarding breast cancer risk or recurrence, based on long-term observational data. Soy intake consistent with a traditional Japanese diet (2–3 servings daily, containing 25–50 mg isoflavones) may protect against breast cancer and recurrence. Human studies show that soy neither increases circulating oestradiol nor affects oestrogen-responsive target tissues. Prospective data on soy use in women taking tamoxifen do not indicate an increased risk.¹⁸

The study by Busby et al. (2002) investigated the safety and pharmacokinetics of purified, unconjugated genistein, daidzein and glycitein after a single dose in 30 healthy men. The administered genistein doses (1, 2, 4, 8 or 16 mg/kg body weight) were higher than those previously administered in humans. Formulation A consisted of 90 ± 5 % genistein, 10 % daidzein and 1 % glycitein; formulation B of 43 % genistein, 21 % daidzein and 2 % glycitein. No clinically significant behavioural or physical changes were observed. Increases in lipoprotein lipase and hypophosphataemia occurred, possibly treatment-related, but without clinical toxicity. Substantial amounts of isoflavones were excreted as conjugates in urine. Mean elimination half-lives were 3.2 h for free genistein and 4.2 h for free daidzein; mean pseudo-half-lives were 9.2 h for total genistein and 8.2 h for total daidzein.⁴¹

The study by Hargreaves et al. (1999) investigated the effect of 14-day soy supplementation with 60 g (45 mg isoflavones) on the normal breast in 84 premenopausal patients. Serum concentrations of genistein, daidzein and equol were increased after supplementation ($p \leq 0.025$). Levels of genistein and daidzein in nipple aspirate fluid were higher than paired serum levels, both before ($p < 0.001$ and $p = 0.001$ respectively) and after supplementation ($p < 0.001$ and $p = 0.049$ respectively); however, there was no significant increase in isoflavone levels in nipple aspirate fluid in response to soy. Levels of apolipoprotein D in nipple aspirate fluid were significantly decreased and pS2 levels increased ($p \leq 0.002$), indicating an oestrogenic stimulus. No effect of soy supplementation was found on breast epithelial cell proliferation, oestrogen and progesterone receptor status, apoptosis, mitosis or Bcl-2 expression. The authors conclude that short-term dietary soy has a weak oestrogenic response in the breast, as measured by nipple aspirate apolipoprotein D and pS2 expression.⁴²

The controlled study by McMichael-Phillips et al. (1998) investigated the effect of daily soy supplementation with 60 g (45 mg isoflavones) for 14 days on the proliferation rate of premenopausal, histologically normal breast epithelium and progesterone receptor expression in 48 women with benign or malignant breast disease. Women were randomised to either their normal diet or this plus soy supplement. Biopsy samples of normal breast were labelled with [3H]thymidine to detect S-phase cells and immunostained for the proliferation antigen Ki67. Serum concentrations of genistein and daidzein rose in the soy group after 14 days. A strong correlation was found between Ki67 and the thymidine labelling index ($r = 0.868$; $p \leq 0.001$). The proliferation rate of mammary epithelium increased.

The analysis and commentary by Messina and Wood (2008) discusses the controversy surrounding soy isoflavones, oestrogen therapy and breast cancer risk. The authors conclude that there is little clinical evidence that isoflavones increase breast cancer risk in healthy women or worsen the prognosis of breast cancer patients. Although relatively limited research has been conducted and clinical studies often included small participant numbers, no harmful effect has been shown.⁴³

The review by Ganai and Farooqi (2014) discusses molecular mechanisms of soy isoflavones in prostate cancer. The predominant and biologically most active isoflavones in soy products – genistein, daidzein, equol and glycitein – inhibit prostate carcinogenesis in some animal models. Cell-based studies show that soy isoflavones regulate genes that control the cell cycle and apoptosis. The authors discuss the literature on molecular events that could explain the benefit of soy isoflavones in the prevention or treatment of prostate cancer.⁴⁷

The review by Spagnuolo et al. (2019) analyses molecular mechanisms of genistein in cancer. Genistein is one of the known isoflavones found in various soy beans and soy products. Its chemical name is 4',5,7-trihydroxyisoflavone. The mechanistic insight shows potential for apoptosis induction, cell cycle arrest as well as anti-angiogenic, anti-metastatic and anti-inflammatory effects in preclinical models. The review covers various molecular mechanisms in diverse cancer models.⁴⁵

HYPOTHESIS The observed oestrogenic effects on the normal breast in short-term studies could indicate weak oestrogen receptor-mediated signalling, yet the clinical relevance for breast cancer development is unclear. Long-term studies with clinical endpoints are lacking; the question whether isoflavones are safe in women with existing breast cancer is not conclusively clarified.

Skin

It reports that soy alleviates hot flushes and may beneficially influence kidney function, relieve depressive symptoms and improve skin health. The work highlights that soy foods are unique sources of isoflavones, which are classified as phytoestrogens and selective oestrogen receptor modulators.⁴⁴

HYPOTHESIS The statement on skin health is based on reviews, not on specific clinical studies with skin endpoints. Whether isoflavones directly alter skin structure or function is an open question that would require controlled studies with objective skin measurements.

Oxidative Stress

The authors report that soy isoflavones regulate genes that control the cell cycle and apoptosis, and that further chemoprotective mechanisms such as antioxidant defence, DNA repair, inhibition of angiogenesis and metastasis, potentiation of radio- and chemotherapeutics as well as antagonism of oestrogen- and androgen-mediated signalling pathways should be considered.⁴⁷

HYPOTHESIS The antioxidant mechanisms are predominantly derived from in-vitro and animal models; their transferability to humans is unclear. Clinical studies with validated biomarkers for oxidative stress are still pending.

Overall Picture

Across all areas a pattern emerges: the evidence on soy isoflavones is heterogeneous. For bone and joints there are several randomised controlled trials with differing results – some show favourable effects on bone density in postmenopausal women with low baseline bone density, others none. For menopausal symptoms meta-analyses indicate a significant reduction in hot flush frequency, whereas the Kupperman Index shows no significant effect. For heart and circulation there are indications of an improvement in arterial stiffness, yet the mechanisms and the responsible isoflavones remain unclear. For metabolism and bioavailability smaller studies exist that show partly positive, partly neutral results. The safety data from review articles and short-term studies are reassuring, yet long-term data on high doses are lacking.

Where clinical endpoints such as fractures, cardiovascular events or cancer incidence are concerned, research is still pending. Many studies use surrogate markers such as bone density, blood lipids or PSA. The role of the gut microbiota and the equol-producer phenotype is increasingly discussed, but has not yet been examined in intervention studies with clinical endpoints. The transferability of the results to men, premenopausal women and different ethnic groups is limited. Open questions concern the optimal dose, the composition of the isoflavones and long-term safety.

Methodology of the Evidence Base

The supporting works comprise randomised controlled trials, crossover studies, observational studies and review articles. Typical endpoints are bone density, blood lipids, hot flush frequency, hormonal parameters, PSA, bioavailability parameters and safety markers. Surrogate markers are frequently used instead of clinical endpoints. The study populations are predominantly postmenopausal women; some studies include men or premenopausal women. Isoflavone doses vary widely (e.g. 40–200 mg/day) and the compositions differ (genistein, daidzein, glycitein, biochanin A, formononetin). Long-term studies with clinical endpoints, studies on the role of the gut microbiota and direct comparisons of different isoflavone preparations are still pending.

The Equol-Producer Thesis

A widespread assumption holds that the health effects of soy isoflavones depend substantially on equol-producer status. This thesis is supported by the observation that S-equol exhibits a higher binding affinity for oestrogen receptor beta than its precursor daidzein. The most-cited work on the subject (325× cited, 2005) describes S-equol as the exclusive enantiomer produced by the human gut flora. A further frequently cited work (279×, 2019) summarises the presumed health benefits of equol. However, these statements rest predominantly on mechanistic and observational data, not on controlled studies that directly compare equol producers and non-producers.

The practical consequence of this thesis would be that part of the population benefits less from isoflavones. Whether this is actually the case, however, has not been conclusively clarified. Many controlled studies report their results without stratifying by equol status. In addition, there are indications that other metabolites or the gut flora as a whole may also play a role. The open question is whether equol status is a valid predictor of the effect of isoflavones and whether it should be routinely recorded in future studies.

3. How Robust the Research Is

Research on soy isoflavones is broad. The majority of human studies consist of controlled trials, a smaller proportion of observational studies. The controlled trials are distributed across numerous application areas, including metabolism, cardiovascular, safety, bone, oncology, cognition, bioavailability, inflammation, gut and antioxidant effects. This distribution shows that the isoflavones have been investigated in many areas without any single dominant application area emerging. The most-cited controlled studies address cognitive function, bone density, plasma lipids, hot flushes, arterial stiffness and the bioavailability of different forms.

Methodologically the field is heterogeneous. Many controlled studies examine soy protein or soy foods in which isoflavones are only one component alongside proteins and other constituents. Others use isolated or synthetic isoflavones. This heterogeneity complicates generalisation. In addition, equol producers constitute only a portion of study participants and this status is often not recorded. The numerous review articles and meta-analyses, for example on menopausal symptoms or hormone concentrations, point to a growing interest in summarising the evidence; the field is comparatively well researched.

4. What Is Frequently Claimed — and What the Data Support

STATEMENT	EVIDENCE BASE
Hot flushes in the menopause	Several controlled studies and meta-analyses investigate this area. The results are inconsistent; the database contains both positive and negative findings. A
Bone density	Controlled studies in postmenopausal women show partly favourable effects on bone density, especially in women with low baseline density. The applicability
Cardiovascular parameters	Studies on plasma lipids and arterial stiffness show improvements in some controlled investigations. The clinical relevance for cardiovascular events is not clear
Cognitive function	A highly cited controlled study (cited 278 times, 2004) investigated cognitive function, bone density and lipids in postmenopausal women. The results are mixed

5. Profile: Molecule and Charge

Soy isoflavones (genistein, daidzein) are not a single molecule but a **mixture** — there is no molecular formula and no fixed molecular mass. What can be described are functional groups, charge behaviour and redox properties; this is precisely the subject of the next section.

6. Charge, Electrons, Radicals

The material provides only few direct statements on the electrochemistry of soy isoflavones. In one human observation genistein is associated with inhibition of reactive oxygen species (ROS), alongside NF-κB, prostaglandins, iNOS and pro-inflammatory cytokines ²⁶. A review article classifies isoflavones in general as radical scavengers and also mentions binding to oestrogen receptors as well as modulation of signalling pathways, enzymes and cytokines ²⁸. One human observation cites reactions to ROS as one of several vascular processes that could delay the progression of atherosclerosis ²⁷. These statements describe effects on radicals, not the charge or redox potential of the molecule itself.

No evidence sentence is found for electron transfer and cation exchange. A cell-culture study distinguishes chlorinated isoflavones from polyphenols that are converted to quinones or epoxides and form adducts with glutathione; the chlorinated isoflavones do not react with GSH but are converted to β-glucuronides and excreted via the bile ²⁹. An environmental study reports for a plant material a positive correlation of total phenol content with DPPH radical scavenging (r = 0.787) and FRAP (r = 0.676) ³⁰; this does not concern genistein or daidzein in humans. A controlled human study mentions the C-3 hydroxyl group in flavonols and intramolecular hydrogen bonds ²⁵, thus a different substance group. It would need to be examined whether charge state, cation exchange and electron transfer of genistein and daidzein can be measured directly.

7. Interactions with Other Substances

Other substances on the platform with which this substance has been **jointly** investigated or discussed in human studies and reviews — combination, comparison or shared pathway of action. The figure denotes the works in which both appear.

SUBSTANCE	SHARED WORKS	OF WHICH CONTROLLED IN HUMANS
Chronic Inflammation	47	23
Art Therapy	41	12
Cognitive Behavioural Therapy for Insomnia (CBT-I)	31	18
High-Intensity Interval Training (HIIT)	31	17
Gut Microbiome	20	6
Stress, Cortisol and Inflammation	18	7
Green Tea and EGCG	14	6
Vitamin D	13	10
Anthocyanins (Berries)	12	1
Therapeutic Fasting and Intermittent Fasting	12	9

Absorption depends on the sugar component: despite higher daidzein content in the aglycone tablets, the AUC for equol was significantly higher after intake of the glucoside tablets, presumably due to the metabolic activity of the gut bacteria during prolonged intestinal transit; the apparent bioavailability of genistein and daidzein did not differ between aglycone and glucoside form in American women ³. Age, sex and food matrix were examined for both forms in

soya milk, textured vegetable protein and tempeh⁷. In five equol excretors, soya increased equol excretion; the combination raised it by a further 58 % (P = 0.0001)³².

Combinations with medicines and nutrients were examined: one study investigated the bioavailability of levothyroxine after oral administration of a fixed soya isoflavone combination in postmenopausal women³⁴, another the co-administration of soya isoflavones and vitamin D³¹. When isoflavones, prenylflavonoids and lignans were given together, their bioavailabilities remained unchanged, yet the phytoestrogen-derived 17beta-oestradiol equivalents were lower³³. Isoflavone preparations combined with exercise did not significantly increase bone density in postmenopausal women in four RCTs with 609 participants^{35 35}. It remains open which dose of a fixed combination alters levothyroxine uptake³⁴.

8. Overdosage, Tolerability, Limits

543 works were examined; 15 RCTs met the inclusion criteria; Kupperman index, hot-flush frequency and adverse events were recorded⁵. A meta-analysis of the five studies with adverse-event data showed no significant difference between groups (p = 0.175)⁵. At 900 mg/day of unconjugated soya isoflavones, very few adverse events occurred in healthy postmenopausal women; substance-related events were mild or grade 1³⁸. At 80–120 mg soya isoflavones from hypocotyl over 2 years, two serious events were recorded (breast carcinoma, oestrogen-receptor-negative endometrial carcinoma), fewer than the expected population rate³⁷.

For breast-cancer patients there is no clear evidence of harm; before high-dose isoflavones (≥ 100 mg) can be recommended, better safety confirmation is required¹⁸. In a 12-week investigation plasma isoflavones rose (P < 0.001) without clinical toxicity; SHBG, total oestradiol and testosterone did not differ significantly from men under placebo^{39 39}. At 100 mg/day the administration was described as well tolerated, yet placebo participants were faster in two tests of executive function (P < 0.05)³⁶. It remains to be clarified whether this difference is reproducible and whether it occurs in a dose-dependent manner.

9. The Most Robust Works

Ordered by strength of evidence, not by familiarity. The complete evaluation comprises considerably more works; the most robust ones are listed here.

Controlled Human Studies

- ¹ Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized ... (2004)
- ² Isoflavone phytoestrogens consumed in soy decrease F(2)-isoprostane concentrations and increase resistance of low-density lipoprotein to oxidation in ... (2000)
- ³ Bioavailability of soybean isoflavones from aglycone and glucoside forms in American women (2003)
- ⁴ Effect of soy phytoestrogens on hot flashes in postmenopausal women with breast cancer: a randomized, controlled clinical trial (2002)
- ⁵ Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review (2015)
- ⁶ The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial (2004)
- ⁷ Factors affecting the bioavailability of soy isoflavones in humans after ingestion of physiologically relevant levels from different soy foods (2006)
- ⁸ Isoflavones reduce arterial stiffness: a placebo-controlled study in men and postmenopausal women (2003)
- ⁹ Soy isoflavones improve plasma lipids in normocholesterolemic, premenopausal women (2000)
- ¹⁰ Effects of soy protein and isoflavones on circulating hormone concentrations in pre- and post-menopausal women: a systematic review and meta-analysis (2009)
- ¹¹ Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: systematic review and meta-analysis of randomized ... (2012)
- ¹² Hydrolysis of isoflavone glycosides to aglycones by beta-glycosidase does not alter plasma and urine isoflavone pharmacokinetics in postmenopausal ... (2002)
- ¹³ Combined inhibitory effects of soy isoflavones and curcumin on the production of prostate-specific antigen (2010)
- ¹⁴ Soy isoflavones have a favorable effect on bone loss in Chinese postmenopausal women with lower bone mass: a double-blind, randomized, controlled ... (2003)
- ¹⁵ Soy isoflavones in the prevention of menopausal bone loss and menopausal symptoms: a randomized, double-blind trial (2011)
- ¹⁶ The effect of isoflavones extracted from red clover (Rimostil) on lipid and bone metabolism (2001)
- ¹⁷ RETRACTED: Psychological assessment of the effects of treatment with phytoestrogens on postmenopausal women: a randomized, double-blind, crossover ... (2006)
- ¹⁸ Soy, red clover, and isoflavones and breast cancer: a systematic review (2013)
- ¹⁹ Influence of 10 wk of soy consumption on plasma concentrations and excretion of isoflavonoids and on gut microflora metabolism in healthy adults (2004)
- ²⁰ Natural S-equol decreases bone resorption in postmenopausal, non-equol-producing Japanese women: a pilot randomized, placebo-controlled trial (2011)
- ²¹ Positive effect of dietary soy in ESRD patients with systemic inflammation--correlation between blood levels of the soy isoflavones and the ... (2006)
- ²² Effect of soy-derived isoflavones on hot flushes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries (2003)

- ²³ Urinary isoflavonoid excretion in humans is dose dependent at low to moderate levels of soy-protein consumption (1997)
- ²⁴ Randomized, double-blind, placebo-controlled crossover study in men with prostate cancer and rising PSA: effectiveness of a dietary supplement (2005)

10. Summary

For the frequency of hot flushes, two meta-analyses consistently support a reduction: Taku et al. (2012) included 17 studies and found a significant decrease under soy isoflavones with a median of 54 mg aglycone equivalents over 6 weeks to 12 months. Chen et al. (2015) evaluated 15 randomised controlled trials and also reported a significantly greater reduction in hot flush frequency, while the Kupperman Index showed no significant treatment effect ($p = 0,110$). Hooper et al. (2009) summarised 47 studies: In premenopausal women, FSH and LH decreased by about 20 %, estradiol, estrone and SHBG remained unaffected; in postmenopausal women, no statistically significant hormone effects were observed.

The connection between gut flora and effect is plausible. Daidzein is converted to S-equol, a metabolite with higher affinity for oestrogen receptor beta, by only some people; depending on the population, this is between one third and half. **Hypothesis:** This inter-individual difference could explain why clinical studies yield inconsistent results, and argues for recording equol-producer status as a characteristic in future. It is equally plausible that some of the observed effects on bone, vascular and metabolic parameters do not originate from the isoflavones themselves, but from the accompanying protein matrix of the soy products used; the inconsistent bone findings could additionally be related to composition, baseline bone density and ethnic origin of the participants.

To be clarified would be an intervention study that specifically promotes equol-producing gut bacteria and compares the effect of isoflavones in equol producers and non-producers with microbial characterisation. It also remains open whether the bone and vascular effects are due to the isoflavones themselves or to the protein matrix; studies with isolated isoflavones without protein carrier would be required here. For menopausal symptoms, a direct comparison of different isoflavone doses and compositions is still pending, as are long-term observations on higher doses and special risk groups. A study that captures dose, composition and equol status together would clarify the question of which preparation works for which persons.

Soy isoflavones are well-studied phytoestrogens whose effect depends strongly on whether the gut flora can convert daidzein to S-equol.

11. What Remains Open

- **Equol Status:** Is the equol-producer status a valid predictor for the effects of soy isoflavones, and should it be routinely recorded in studies?
- **Long-term Effects:** What effects do soy isoflavones have on clinical endpoints such as fractures or cardiovascular events with long-term intake?
- **Comparability:** How can results from studies with soy protein, isolated isoflavones and synthetic forms be meaningfully compared?

12. Further Paths

Topics, modes of action and pathways in which this substance occurs — for all those who wish to look beyond the substance.

- Interaction Network

Frequently Asked Questions

Are soy isoflavones equally effective for all people?

No, the effect seems to vary individually. An important factor is the intestinal flora: Only some people can convert daidzein to S-equol, a metabolite with higher oestrogenic activity. Whether this status significantly determines the health effects is the subject of ongoing research.

What role does the dosage form play for the study situation?

A major role. Many studies use soy protein or soy foods, in which isoflavones are only one of many components. Others use isolated or synthetic isoflavones. These differences make it difficult to compare the results and explain part of the heterogeneity.

Are there indications of undesirable effects?

Controlled studies examine safety aspects. So far, no serious undesirable effects have been reported at usual dosages. However, long-term data on very high dosages or in risk groups are still outstanding.

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