Abstract

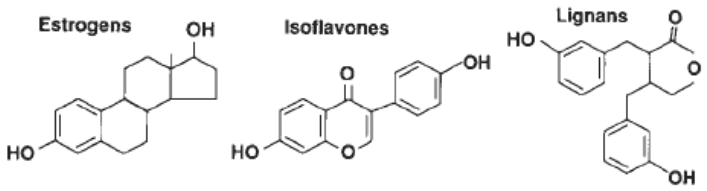
Genistein is a phytoestrogen (estrogen-like chemical compound present in plants) that binds to estrogen receptors and has both weak estrogenic and weak anti-estrogenic effects. There are three major classes of phytoestrogens that have estrogen-like actions in the human body. They are lignans, isoflavones, and coumestans. Genistein is an isoflavone. Exposure to genistein occurs principally through foods made with soybeans and soy protein. Genistein has been found in breast milk and is available via soy milk. It is possible that genistein influences early onset of puberty in girls, but more research needs to be conducted. Exposure to genistein can be measured using a blood or urine test; however, levels vary widely in each person due to considerable variability in the metabolism of genistein. *In vitro* studies with high concentrations of genistein demonstrate inhibition of cell proliferation while under some conditions low concentrations stimulate cell proliferation. *In vivo* studies demonstrate that genistein inhibits chemically-induced mammary cancer rats while others report that it stimulates growth of cancer cells in immune deficient rodent models. Epidemiologic studies have found conflicting evidence; some studies have found an association between soy exposure and decreased breast cancer risk while others have found no association. Some epidemiological evidence indicates that soy intake may be more protective when the exposure occurs prior to puberty. More research needs to be conducted on the association between breast cancer risk and genistein specifically before conclusions can be drawn. The International Agency for Research on Cancer (IARC) has not determined whether phytoestrogens are carcinogenic to humans.

This fact sheet provides information about genistein, one of three phytoestrogens being measured and examined by the Breast Cancer and the Environment Research Centers (BCERC) epidemiology studies, sources of exposures, effects on puberty, effects in the body, and research studies looking at genistein as being associated with breast cancer risk.

What is genistein?

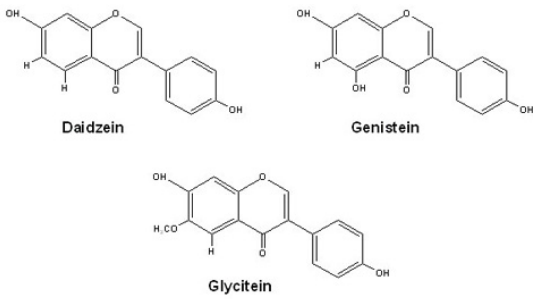
Genistein is a phytoestrogen (estrogen-like chemical compound present in plants) that is derived from certain plant precursors by human metabolism. They are naturally occurring chemical constituents that may interact with estrogen receptors to produce weak estrogenic or anti-estrogenic effects. They are composed of a wide group of nonsteroidal compounds similar in structure and function to human estrogens (1). A conspicuous feature of the chemical structure of phytoestrogens is the presence of a phenolic ring that, with few exceptions, is a prerequisite for binding to the estrogen receptor (Fig. 1). For this reason, phytoestrogens can act as weak estrogen agonists, partial agonists, or as antagonists to endogenous estrogens (such as estradiol) and xenoestrogens (including phytoestrogens) with estrogen receptors in both animals and humans. Therefore, working as estrogen mimics, phytoestrogens may either have the same effects as estrogen or block estrogen's effects. There are three major classes of plant chemical compounds that have estrogen-like actions in the body. They are lignans (enterolactone, enterodiol), isoflavones (genistein, daidzein, biochanin A), and coumestans. The two major chemical classes of phytoestrogens found in people's diets are lignans (enterodiol and enterolactone) and isoflavones (daidzein, genistein, and glycitein). Lignans are the main class of phytoestrogens present in Western diets. Genistein is an isoflavone.

Figure 1:



Isoflavones are a subgroup of flavinoids. Among commonly consumed foods, isoflavones are found in dietary-relevant amounts only in the soybean. The two primary isoflavones in soybeans are daidzein and genistein and their respective glucosides genistin and daidzin (Fig. 2). Soy foods typically contain more genistein than daidzein, although this ratio varies among different soy products.

Figure 2:



The terms “soy” and “soybean” are commonly used for the leguminous Asian plant *Glycine max*. Soybean is also used to designate the edible seed of this plant. In this fact sheet, the term “soy” is used as an adjective to denote products derived from the edible seed (e.g., soy milk, soy formula, soy meal) and soybean is used to refer to the edible seed itself.

The common biological roles of phytoestrogens are to protect plants from stress and to act as part of a plant’s defense mechanism. Some ecologists postulate that phytoestrogens may have evolved to protect the plants by interfering with the reproductive ability of grazing animals (2).

How are humans exposed to genistein?

Ingestion is the source of human exposure to genistein. Exposure occurs principally through food, infant formulas, and/or dietary supplements made with soybeans and soy protein, but not soy oils. All soybean foods and proteins currently available for human consumption contain significant amounts of the isoflavones genistein and daidzein, either as the aglycone (unconjugated form) or as different types of glycoside conjugates.

Ingestion

- **Food**
  Leguminous plant foods contain genistein. Soybeans, a cholesterol-free, high protein legume, contain the most genistein. Other legumes, such as chickpeas (garbanzo beans), contain small amounts of genistein. Genistein can be found in many food products containing soy such as soy-based infant formulas, tofu, soymilk, soy flour, textured soy protein, soy protein isolates, tempeh, and miso, as well as over-the-counter dietary supplements. Often, soy flour is used for fortification of other flours, including wheat, rice, and corn. The genistein content of these products is quite variable.

  Soy flour contains 53% soy protein. Textured Soy Protein (TSP), a meat substitute made from defatted soy found in hamburgers, sausages, hot dogs, meatballs, meat loafs, can contain 50% to 70% soy protein, depending on the starting soy material used. Soy Protein Isolates (SPI), used in the preparation of specialty nutrition foods such as infant formulas, sports drinks, bodybuilding beverages, energy bars, and special diets for the very sick, contain 90% soy protein. Soy oil and soy sauce contain little to zero genistein.

  Other plant foods that have been shown to contain genistein include alfalfa and clover sprouts, barley meal, broccoli, cauliflower, and sunflower, caraway, and clover seeds.

Total Isoflavone, Daidzein and Genistein Aglycone Content of Selected Foods				
Food	**Serving**	**Total Isoflavones (mg)**	**Daidzein (mg)**	**Genistein (mg)**
Soy protein concentrate, aqueous washed	3.5 oz	102	43	56
Soy protein concentrate, alcohol washed	3.5 oz	12	7	5
Miso	½ cup	59	22	34
Soybeans, boiled	½ cup	47	23	24
Tempeh	3 ounces	37	15	21
Soybeans, dry roasted	1 ounce	37	15	19
Soy milk	1 cup	30	12	17
Tofu yogurt	½ cup	21	7	12
Tofu	3 ounces	20	8	12
Soybeans, green, boiled (Edamame)	½ cup	12	6	6
Meatless (soy) hot dog	1 hot dog	11	3	6
Meatless (soy) sausage	3 links	3	0.6	2
Soy cheese, mozzarella	1 oz	2	0.3	1

Source: http://lpi.oregonstate.edu/infocenter/phytochemicals/soyiso/index.html#source

- **Infant Formulas**

  Soy-based infant formulas have been commercially available since the mid 1960s (3). The formulas are made from soy protein isolate (SPI) and contain significant amounts of soy isoflavones. In 1997,the total isoflavone content of soy-based infant formulas commercially available in the US ranged from 32-47 mg/liter (~ 34 fluid ounces) (4).

  Infants are able to absorb isoflavones, and infants fed soy formula were demonstrated to have plasma isoflavone blood levels exceeding those of Japanese adults several-fold (5). Soy-based infant formula can result in plasma concentrations of isoflavones in infants that are 13,000 - 22,000 times higher than endogenous estrogen concentrations in infants (6). Infants consuming soy-based formula are exposed to 6-11 mg/kg per day of isoflavones (4-7 mg/kg per day of total genistein) that result in circulating levels of approximately 1-5 µM of total genistein. In contrast, adults consuming a moderate to large amount of soy in the diet are exposed to ~1 mg/kg per day of total genistein resulting in circulating levels of approximately 0.5 µM of total genistein (7). Even though infants ingesting soy milk are exposed to high concentrations of genistein, little toxicity has been reported. The most noted consequence is hypothyroidism in infants with compromised thyroid function.

Total Isoflavone, Daidzein and Genistein Aglycone Content of Selected Soy-based Infant Formulas				
Soy-based Formula	**Serving**	**Total isoflavones (mg)**	**Daidzein (mg)**	**Genistein (mg)**
Mead Johnson Prosobee, ready to feed	8 fl oz	9.4	4.1	5.3
Ross Isomil, ready to feed	8 fl oz	10.2	4.7	5.5
Wyeth-Ayerst Nursoy, ready to feed	8 fl oz	6.4	1.8	3.9

Source: http://lpi.oregonstate.edu/infocenter/phytochemicals/soyiso/index.html#sources

- **Dietary Supplements**

  Dietary supplements containing genistein are available in the US without a prescription. These products are not standardized, and the amounts of soy isoflavones they provide may vary considerably. For example, in an analysis of a soy supplement purchased at a local health food store containing genistein, the genistein content measured was 1.4 mg/tablet; the value represented 48% of the genistein level listed on the product label (8).

  Genistein is mainly present in the form of its glycoside genistin in supplements. It is found in capsules, powder, and tablets. Some genistein supplements contain genistein which has been

hydrolyzed in a chemical process. Tablets contain up to 20 mg genistein (9). Supplements that are labeled as 1000 mg relate to soybean content.

Women with estrogen receptor-positive tumors are advised to exercise caution in the use of genistein/genistin supplements and should only use them if they are recommended and monitored by a physician (20).

- **Water**
  Not a significant route of exposure. Genistein is a solid substance that is practically insoluble in water.

Inhalation
Not a significant route of exposure.

Intravenous
Not a significant route of exposure.

Skin Absorption
Not a significant route of exposure.

How does genistein work in the human body?

Genistein is an isoflavone aglycone and is produced in the body from plant isoflavones. Isoflavones are contained in soybean or soy foods in two chemical forms, i.e., aglycones (uncongugated form) and glucosides (bound to a sugar molecule). The main dietary source of genistein is the biologically active glucoside genistin. Fermentation or digestion of soybeans or soy products results in the release of the sugar molecule from the isoflavone glycoside, genistin, leaving the isoflavone aglycone, genistein (10). Before genistein can act it first needs to be released from genistin. This normally happens in the stomach (acid hydrolysis) and intestine (action of bacterial enzymes).

There is considerable individual variation in the absorption and metabolism of ingested genistin and genistein. There are some data suggesting that genistein may be more bioavailable than genistin. However, other data suggest that the extent of absorption of genistein is similar for the aglycone and the glucoside forms. There is little data available on the tissue distribution of genistein. The pharmacokinetics of genistein in humans is complex and not well understood.

Genistein affects the process by which signals at the cell surface are transferred to the interior of the cell and inhibits the activity of several enzymes intimately involved in controlling cell growth and regulation (11). The complete metabolic fate of exposure to genistein is not known.

Genistein is the most studied of the soy isoflavones with regard to antioxidant activity. It is thought that genistein may be a more potent antioxidant than daidzein (12). There are few studies comparing the antioxidant activity of the two isoflavones (13).

Is genistein an endocrine disruptor?

Perhaps.

Endocrine disruptors are exogenous synthetic or natural chemicals that can mimic or modify the action of endogenous hormones. Isoflavones bind to both estrogen receptors (ER α and ER β), however, they preferentially bind to and activate ER β (14). For this reason, they are sometimes classified as selective estrogen receptor modulators (SERMs). At concentrations that are achieved from dietary soy exposures, genistein has been found to have both weak estrogenic and weak anti-estrogenic effects (15). *In vivo*, genistein's estrogenic activity is one-third that of glycitein and four times greater than that of daidzein (16).

Does genistein exposure influence onset of puberty in girls?

Unknown. BCERC's biology and epidemiology studies are investigating this question.

Some evidence indicates that *in utero* and prepubertal exposure to genistein accelerates puberty onset in rodents (17, 18). One study also found that neonatal injections of genistein exposure influenced subsequent mammary gland development in mice, depending on the dose used. Mice

injected with 50 mg/kg.d of genistein had stunted mammary gland development, whereas mice injected with 0.5 mg/kg.d of genistein exhibited advanced mammary gland development (19). On the other hand, genistein fed in the diet to rats at concentrations that yield similar blood levels as humans eating a diet high in soy enhances mammary gland differentiation and suppresses chemically-induced mammary cancer and results in no toxicity (20). Ingesting genistein, as opposed to injecting it, alters bioavailability and mechanism of action.

The BCERC epidemiology study entitled "Environmental and Genetic Determinants of Puberty" completed a small pilot study in November 2006 and measured genistein in young girls urine. The pilot study completed in November 2006 examined urinary biomarkers in ninety peripubertal Asian, Black, Hispanic and White girls to determine exposures to three chemical families known or likely to possess hormonal activity that may be estrogen agonistic or antagonistic (phytoestrogens, phthalate acids, and phenolic compounds). Phytoestrogens as a group had the highest concentrations (21). All six phytoestrogens (Enterolactone, Genistein, Daidzein, Equol, Enterodiol, *O*-DMA) were detected in > 98% of samples collected. The levels of phytoestrogen metabolites were similar to those reported in the NHANES 2001–2002 children (6). The exposures varied by characteristics that may be relevant to development (6). The highest median concentrations for individual analytes in each chemical family were for the phytoestrogen enterolactone (298 µg/L), phthalate acid monoethylphthalate (MEP; 83.2 µg/L), and phenolic compound benzophenone-3 (BP3; 14.7 µg/L) (21). This small pilot data set will guide future expanded cohort studies.

Does genistein cross the placenta?

Yes.

By measuring the levels of genistein at birth in human newborns and umbilical cords, studies have shown that genistein can be transferred from mother to fetus (22, 23). In the US, typical diets are low in soy products, and the fetus is thus hypothesized to be exposed to low levels of genistein. In Asian cultures consuming soy products, the fetus is exposed to genistein as a result of maternal soy product intake, yet little or no toxicity is reported.

Pregnant women are advised to avoid the use of genistein/genistin-containing supplements pending long-term safety studies (24).

Is genistein found to be present in breast milk?

Yes.

The highest concentrations of isoflavones were reported in breast milk from women eating vegan and vegetarian diets (25). Despite the potential for genistein exposure, breast milk remains the best and most complete nutritional source for young infants. Nursing mothers are advised to avoid the use of genistein/genistin-containing supplements pending long-term safety studies (24).

Are concentration levels of genistein the same in men and women?

Yes.

A recent study of 1414 adults from 9 European countries found that plasma concentrations of genistein did not differ significantly in men and women; the mean concentration for men was 1.77 mg/L and the mean concentration for women was 1.70 mg/L (26). In the National Health and Nutrition Examination Survey (NHANES) 2001-2002, females and males also had similar urinary levels of genistein; the mean concentration for males was 32.2 µg/L and the mean concentration for females was 33.7 µg/L (6).

Are there medical tests for genistein exposure?

Yes.

Blood Tests

Phytoestrogens persist in plasma for about 24 hours. The plasma half-life of genistein and daidzein, measured from their plasma appearance and disappearance curves to be 7.9 hours in adults; peak

concentrations occur 6-8 hours after ingestion. Consequently, adherence to a soy-containing diet will ultimately lead to high steady-state plasma concentrations.

Plasma concentrations of 50-800 ng/mL are achieved for daidzein, genistein and equol in adults consuming modest quantities of soy-foods containing in the region of 50 mg/day of total isoflavones. These values are similar to those of Japanese consuming their traditional diet (27).

Urine Tests

Most studies of the metabolism of isoflavones have focused on urinary excretion. This is partly because of the high concentrations found in urine after soy intake and the methodologic difficulties encountered in measuring the lower concentrations in other biological fluids. Few studies have measured circulating concentrations of isoflavones; this reflects the greater difficulty of measurement in plasma compared with urine.

Isoflavones have short-half lives (approximately 8 hours), and nearly all ingested isoflavones are excreted within 24 hours in both urine and feces (28). There is considerable interindividual variation in gut bacterial metabolism of genistein which leads to markedly different urinary concentrations of genistein and its metabolites in different individuals (14). In NHANES 2001-2002, the mean urine concentration for genistein in the total population age 6 and older was 33.0 µg/L. The range from the 50th percentile to the 95th percentile was 28.9-613.0 µg/L (6).

In in vitro studies, what is the association between genistein exposure and breast cancer risk? [An experiment in a test tube or cell culture system is an in vitro experiment.]

Genistein is the most studied of the phytoestrogens. *In vitro* studies have shown that the growth of both estrogen receptor-positive breast cancer cells and estrogen receptor-negative breast cancer cells is inhibited when high levels of genistein (>10µM) are added to the culture medium; however, the growth of estrogen receptor-positive breast cancer cells is actually stimulated when low and physiologically relevant concentrations of genistein are added (14,32). The association between genistein and breast cancer risk *in vitro* is complex and depends on both the concentration of genistein and the concentration of estrogen.

In in vivo studies, what is the association between genistein exposure and breast cancer risk? [An experiment in an animal model is referred to as an in vivo experiment.]

BCERC's laboratory-based biology research project entitled, **"**Environmental Effects on the Molecular Architecture and Function of the Mammary Gland across the Lifespan," is investigating the association between genistein exposure and breast cancer risk. Genistein is the most studied of the phytoestrogens in *in vivo* studies and thus far, rodent studies of genistein and breast cancer risk have had conflicting results. Some studies have shown that genistein inhibits the development and growth of mammary tumors, while other studies have found that genistein stimulates the growth of existing estrogen-sensitive mammary tumors (16).

Evidence indicates that the timing of exposure may be important. Genistein has consistently been shown to inhibit the development of estrogen-sensitive mammary tumors when given to prepubertal rats (15). Genistein has also been shown to accelerate mammary gland development as well as alter mammary gland development following early life exposure (exposures that took place before or around the time of birth or around the time of puberty) in rat models. Effects depend on time and route of exposure (19, 20). A study in 1999 by Hilakivi-Clarke showed an increase in carcinogen-induced mammary cancer in female rat offspring after maternal genistein injection, suggesting that an elevated estrogenic environment *in utero* could increase subsequent breast cancer risk (29). However, genistein administered prenatally in the diet to rats did not increase predisposition for mammary cancer (20)

In epidemiological studies, what is the association between genistein exposure and breast cancer risk? [Studies of diseases in populations of humans or other animals.]

There is no evidence that dietary intake of plant isoflavones is associated with breast cancer risk. There are a limited number of epidemiological studies that have examined the relationship between genistein specifically and breast cancer risk. One 2007 Dutch study found that high plasma levels of genistein were associated with a 32% reduction in breast cancer risk (13).

Evidence from epidemiological studies is conflicting for soy and total phytoestrogen intake. Some case-control and cohort studies have found a protective effect and some have not found any effect. One recent meta-analysis of 18 epidemiologic studies concluded that soy intake may be associated with a small reduction in breast cancer risk (15). In the studies that stratified by menopausal status, the reduction in breast cancer risk was somewhat stronger among premenopausal women. However, the authors also noted that there were methodological problems with many of the studies included in the meta-analysis.

Some epidemiological evidence indicates that soy intake may be more protective when the exposure occurs prior to puberty. One study of Chinese women found that intake of soyfood during adolescence reduced breast cancer risk in a dose-dependent manner (30). The highest quintile of intake reduced risk by 49%.

Was genistein included in biomonitoring measurements from the 1999-2002 National Health and Nutrition Examination Survey (NHANES) Third Report?
Yes.

Urinary levels of phytoestrogens were measured in a subsample of NHANES participants aged 6 years and older (6). Participants were selected within the specified age range to be a representative sample of the U.S. population. In general, the concentrations observed in the NHANES 1999-2000 and 2000-2001 subsamples reflect a diet lower in isoflavones than lignans, consistent with consumption of a Western diet in which whole grains and cereals rather than soybean products contribute the bulk of phytoestrogens. Enterolactone levels were highest followed by daidzein, genistein, enterodiol, equol, and O-desmethylangolensin. Isoflavone levels at the higher percentiles may reflect dietary supplementation with soy products.

In NHANES 2001-2002, both urinary genistein and daidzein levels were higher in the group aged 6 - 11 years than in either of the groups aged 12-19 years or 20 years and older. Females and males had similar urinary levels of genistein.

What has the IARC determined about genistein and carcinogenesis?
The International Agency for Research on Cancer (IARC) has not determined phytoestrogens to be carcinogenic to humans. The IARC is part of the World Health Organization (WHO).

Has the federal government made recommendations to protect human health?
Yes.

FDA
In October 1999, the FDA approved a health claim that can be used on labels of soy-based foods to tout their heart-healthy benefits. The agency reviewed research from 27 studies that showed soy protein's value in lowering levels of total cholesterol and low-density lipoprotein (LDL, or "bad" cholesterol).

Since 1999, food marketers can now use the following claim, or a reasonable variation, on their products: "Diets low in saturated fat and cholesterol that include 25 grams of soy protein a day may reduce the risk of heart disease. One serving of (name of food) provides __ grams of soy protein."

To qualify for the claim foods must contain per serving:

- 6.25 grams of soy protein
- low fat (less than 3 grams)
- low saturated fat (less than 1 gram)
- low cholesterol (less than 20 milligrams)
- sodium value of less than 480 milligrams for individual foods, less than 720 milligrams if considered a main dish, and less than 960 milligrams if considered a meal.

Foods made with the whole soybean, such as tofu, may qualify for the claim if they have no fat other than that naturally present in the whole bean.

NIEHS

An independent panel of 14 scientists was convened in March 2006 by the Center for the Evaluation of Risks to Human Reproduction (CERHR) (31) to evaluate whether genistein or soy formula is hazardous to human development or reproduction.

The final report is available at http://cerhr.niehs.nih.gov/chemicals/genistein-soy/genistein/Genistein_Report_final.pdf (25).

The report found that: "There are no human data available on developmental or reproductive toxicity of purified genistein. Available experimental data are sufficient to conclude that purified genistein can produce reproductive and/or developmental toxicity in rats and mice."

Breast Cancer and the Environment Research Centers Community Outreach and Translation Cores http://www.bcerc.org/cotc.htm

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